Genome wide meta-analysis identifies genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders.

Cross-Disorder Group of the Psychiatric Genomics Consortium*

* Author lists are provided at the end of the manuscript

Corresponding Authors:

Phil H. Lee: plee0@mgh.harvard.edu
Jordan W. Smoller: jsmoller@mgh.harvard.edu

Summary

Genetic influences on psychiatric disorders transcend diagnostic boundaries, suggesting substantial pleiotropy of contributing loci. However, the nature and mechanisms of these pleiotropic effects remain unclear. We performed a meta-analysis of 232,964 cases and 494,162 controls from genome-wide studies of anorexia nervosa, attention-deficit/hyperactivity disorder, autism spectrum disorder, bipolar disorder, major depression, obsessive-compulsive disorder, schizophrenia, and Tourette syndrome. Genetic correlation analyses revealed a meaningful structure within the eight disorders identifying three groups of inter-related disorders. We detected 109 loci associated with at least two psychiatric disorders, including 23 loci with pleiotropic effects on four or more disorders and 11 loci with antagonistic effects on multiple disorders. The pleiotropic loci are located within genes that are disproportionately expressed in the brain throughout the lifespan, beginning in the second trimester prenatally, and play prominent roles in a suite of neurodevelopmental processes. These findings have important implications for psychiatric nosology, drug development, and risk prediction.

Keywords

Psychiatric genetics, cross-disorder genetics, psychiatric disorders, pleiotropy, neurodevelopment, GWAS, genetic correlation, gene expression

Introduction

Psychiatric disorders affect more than 25% of the population in any given year and are a leading cause of worldwide disability (Disease et al., 2017; Kessler and Wang, 2008). The substantial influence of genetic variation on risk for a broad range of psychiatric disorders has been established by both twin and, more recently, large-scale genomic studies (Smoller et al., 2018). Psychiatric disorders are highly polygenic, with a large proportion of heritability contributed by common variation. Many risk loci have emerged from genome-wide association studies (GWAS) of, among others, schizophrenia (SCZ), bipolar disorder (BIP), major depression (MD), and attention-deficit/hyperactivity disorder (ADHD) from the Psychiatric Genomics Consortium (PGC) and other efforts (Sullivan et al., 2018). These studies have revealed a surprising degree of genetic overlap among psychiatric disorders(Brainstorm et al., 2018). Elucidating the extent and biological significance of cross-disorder genetic influences has implications for psychiatric nosology, drug development, and risk prediction. In addition, characterizing the functional genomics of cross-phenotype genetic effects may reveal fundamental properties of pleiotropic loci that differentiate them from disorder-specific loci, and help identify targets for diagnostics and therapeutics.

In 2013, analyses by the PGC's Cross-Disorder Workgroup identified loci with pleiotropic effects across five disorders: autism spectrum disorder (ASD), ADHD, SCZ, BIP, and MD in a sample comprising 33,332 cases and 27,888 controls 'Smoller, 2013 #11061. In the current study, we examined pleiotropic effects in a greatly expanded dataset, encompassing 232,964 cases and 494,162 controls, that included three additional psychiatric disorders: Tourette syndrome (TS), obsessive-compulsive disorder (OCD), and anorexia nervosa (AN). We address four major questions regarding the shared genetic basis of these eight disorders: 1) Can we identify a shared etiologic structure within the broad range of these clinically distinct psychiatric disorders? 2) Can we detect additional loci associated with risk for multiple disorders (pleiotropic loci)? 3) Do some of these risk loci have opposite allelic effects across disorders? and 4) Can we identify functional features of the pleiotropic loci that could account for their broad effects on psychopathology?

Results

We analyzed genome-wide single nucleotide polymorphism (SNP) data for eight neuropsychiatric disorders using a combined sample of 232,964 cases and 494,162 controls (**Table 1; Supplementary Table 1**). The eight disorders included AN 'Duncan, 2017 #12578}, ASD (Grove et al., 2017), ADHD (Demontis et al., 2018), BIP (Stahl et al., 2018), MD (Wray et al., 2018), OCD (International Obsessive Compulsive Disorder Foundation Genetics and Studies, 2018), TS (Yu et al., In press.), and SCZ

(Schizophrenia Working Group of the Psychiatric Genomics, 2014). All study participants were of self-identified European ancestry, which was supported by principal component analysis of genome-wide data.

Table 1. Summary of eight neuropsychiatric disorder datasets

Disorder	Cases	Controls	Total Samples	Population prevalence (k)	Liability-based SNP heritability (SE)	References
ADHD	19,099	34,194	53,293	0.05	0.222 (0.014)	Demontis et al. 2018
AN	3,495	10,983	14,478	0.01	0.195 (0.029)	Duncan et al. 2017
ASD	18,381	27,969	46,350	0.01	0.113 (0.010)	Grove et al. 2017
BIP	20,352	31,358	51,710	0.01	0.182 (0.011)	Stahl et al. 2018
MD	130,664	330,470	461,134	0.15	0.085 (0.004)	Wray et al. 2018
OCD	2,688	7,037	9,725	0.025	0.280 (0.041)	IOCDF-GC and OCGAS
SCZ	33,640	43,456	77,096	0.01	0.222 (0.012)	Schizophrenia Working Group of PGC. 2014
TS	4,645	8,695	13,340	0.008	0.200 (0.026)	Yu et al. 2018
Total	**232,964**	**494,162**	**727,126**			

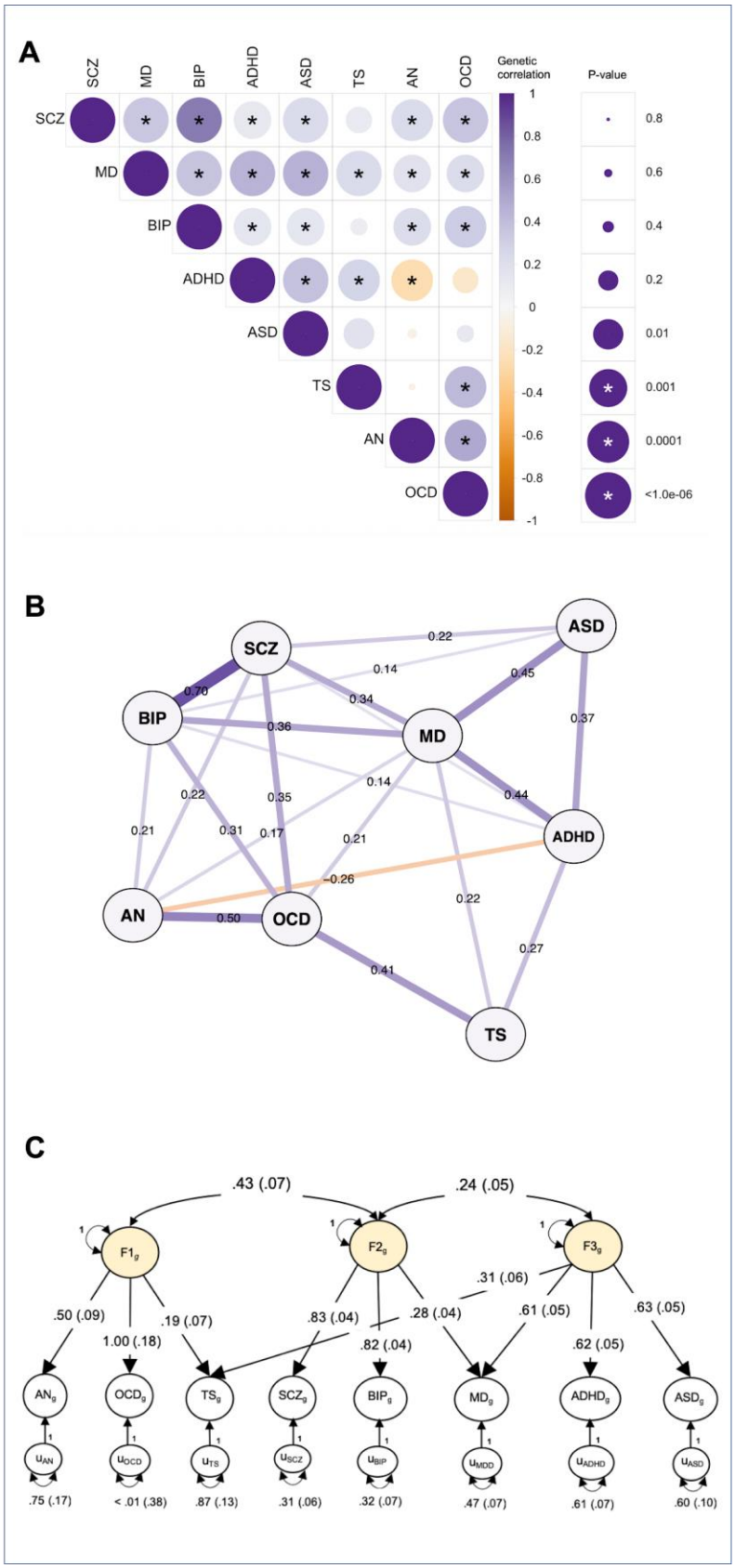
The number of cases and controls used in the meta-analysis of the present study. The numbers may differ from those reported in the original publications because our study included only European ancestry subjects to avoid potential confounding due to ancestral heterogeneity across distinct disorder studies. SNP heritability was estimated from the GWAS summary statistics using LD score regression.

Genetic correlations among eight neuropsychiatric disorders indicate three genetic factors.

After standardized and uniform quality control, additive logistic regression analyses were performed on individual disorders (Online Methods). A total of 6,786,994 SNPs were common across all datasets and were retained for further study. Using the summary statistics of these SNPs, we first estimated pairwise genetic correlations among the eight disorders using linkage disequilibrium (LD) score regression analyses 'Bulik-Sullivan, 2015 #12456} (Online Methods; **Fig. 1a; Supplementary Table 2**). The

results were broadly concordant with previous estimates (Brainstorm et al., 2018) (Cross-Disorder Group of the Psychiatric Genomics et al., 2013). The genetic correlation was highest between SCZ and BIP (r_g = 0.70 ±0.02), followed by OCD and AN (r_g = 0.50 ±0.12). Interestingly, based on genome-wide genetic correlations, MD was closely correlated with ASD (r_g=0.45 ±0.04) and ADHD (r_g=0.44 ±0.03), two childhood-onset disorders. Despite variation in magnitude, significant genetic correlations were apparent for most pairs of disorders, suggesting a complex, higher-order genetic structure underlying psychopathology (**Fig. 1b**).

We modeled the genome-wide joint architecture of the eight neuropsychiatric disorders using an exploratory factor analysis (EFA) (Gorsuch, 1988), followed by genomic structural equation modeling (SEM) (Grotzinger et al., 2018) (Online Methods). EFA identified three correlated factors, which together explained 51% of the genetic variation in the eight neuropsychiatric disorders (**Supplementary Table 3**). The first factor consisted primarily of disorders characterized by compulsive behaviors, specifically AN, OCD, and, more weakly, TS. The second factor was characterized by mood and psychotic disorders (MD, BIP, and SCZ), and the third factor by three early-onset neurodevelopmental disorders (ASD, ADHD, TS) as well as MD. Similar to our EFA results, hierarchical clustering analyses also identified three sub-groups among the eight disorders (**Supplementary Fig. 1**).



1.

Figure 1. Genetic relationships between eight psychiatric disorders.

Cross-disorder meta-analysis identifies 109 pleiotropic loci

The factor structure described above is based on average effects across the genome, but does not address more fine-grained cross-disorder effects at the level of genomic regions or individual loci. To identify genetic loci with shared risk, we performed a meta-analysis of the eight neuropsychiatric disorders using a fixed-effects-based method (Bhattacharjee et al., 2012) that accounts for the differences in sample sizes, existence of subset-specific effects, and overlapping subjects across datasets (Online Methods). There was no evidence of genomic inflation (λ_{1000} = 1.005; **Fig. 2a**). Using the primary fixed-effects-based meta-analysis, we identified 136 LD-independent regions with genome-wide significant association ($P_{meta} \leq 5x10^{-8}$). Due to the known extensive LD at the major histocompatibility complex (MHC) region (chromosome 6 region at 25-35 Mb), we considered the multiple signals present there as one locus. 101 of the 136 (74.3%) significantly associated regions overlapped with previously reported genome-wide significant regions from at least one individual disorder, while 35 loci (25.7%) represented novel genome-wide significant associations.

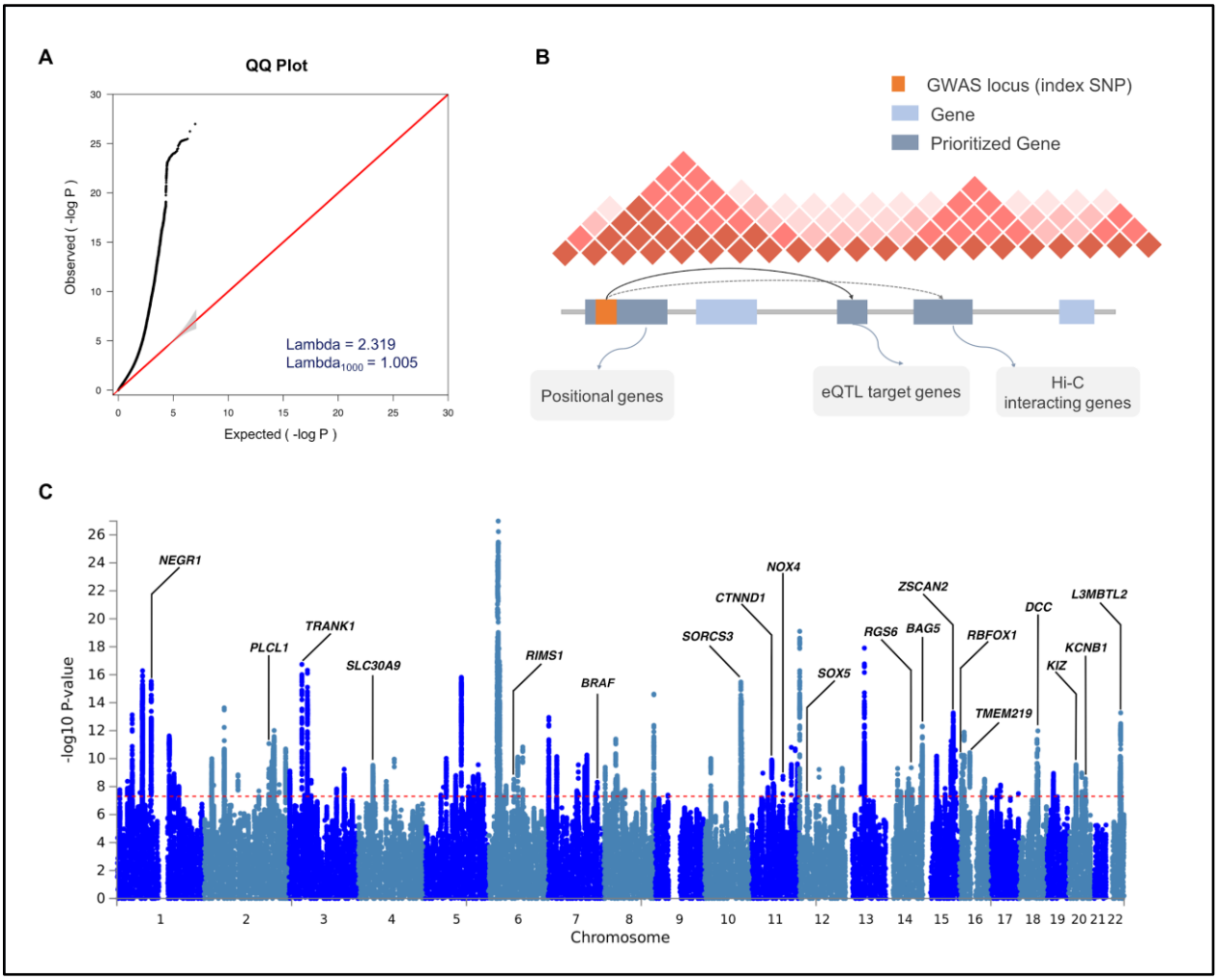


Figure 2. Results of cross-disorder meta-analysis and strategy for mapping loci to genes.

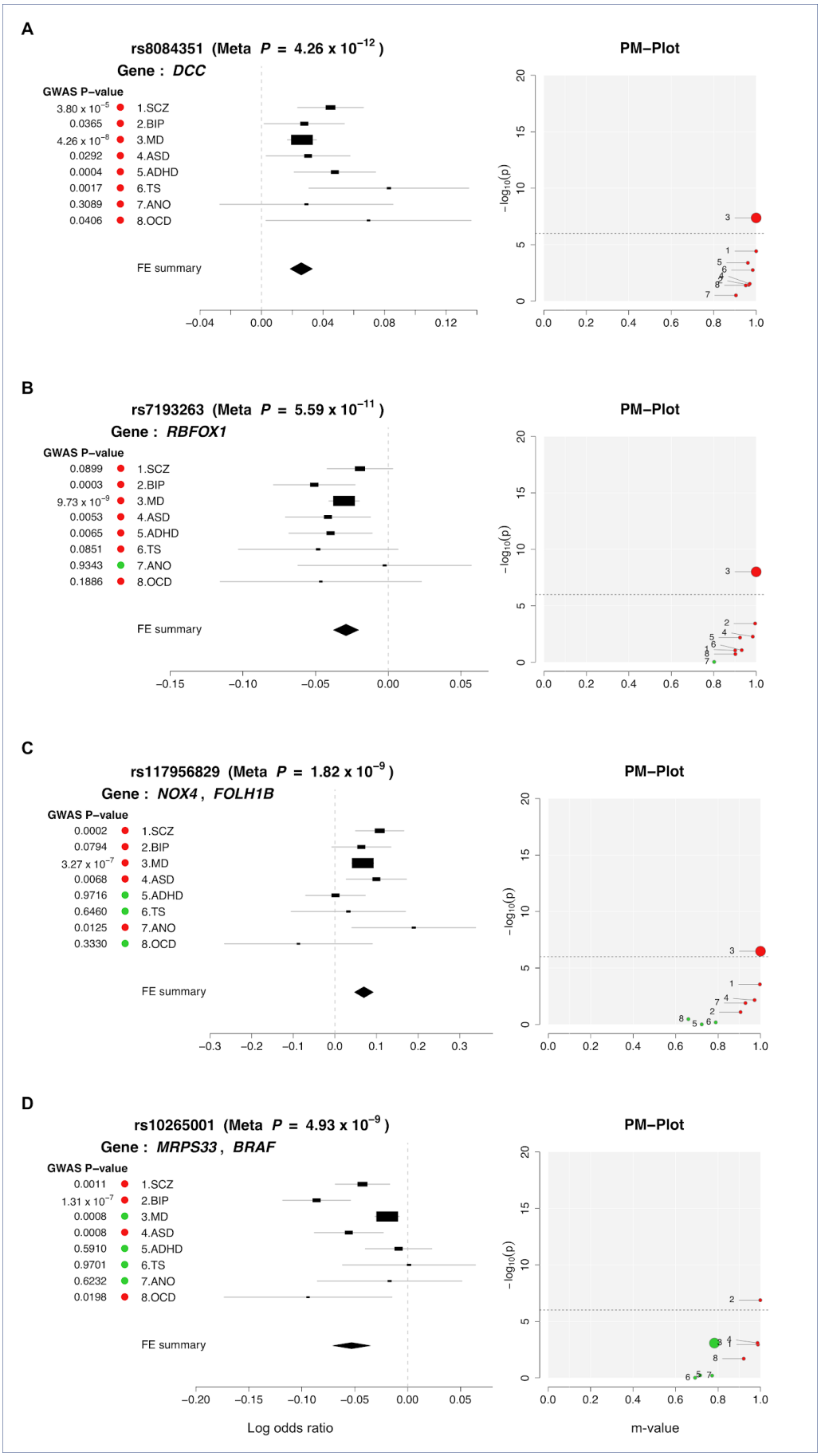

A
rs8084351 (Meta P = 4.26 x 10−12)
Gene : DCC
GWAS P−value
3.80 x 10−5 1.SCZ
0.0365 2.BIP
4.26 x 10−8 3.MD
0.0292 4.ASD
0.0004 5.ADHD
0.0017 6.TS
0.3089 7.ANO
0.0406 8.OCD
FE summary
−0.04 0.00 0.04 0.08 0.12
PM−Plot
−log10(p)
0 5 10 15 20
0.0 0.2 0.4 0.6 0.8 1.0
B
rs7193263 (Meta P = 5.59 x 10−11)
Gene : RBFOX1
GWAS P−value
0.0899 1.SCZ
0.0003 2.BIP
9.73 x 10−9 3.MD
0.0053 4.ASD
0.0065 5.ADHD
0.0851 6.TS
0.9343 7.ANO
0.1886 8.OCD
FE summary
−0.15 −0.10 −0.05 0.00 0.05
PM−Plot
−log10(p)
0 5 10 15 20
0.0 0.2 0.4 0.6 0.8 1.0
C
rs117956829 (Meta P = 1.82 x 10−9)
Gene : NOX4 , FOLH1B
GWAS P−value
0.0002 1.SCZ
0.0794 2.BIP
3.27 x 10−7 3.MD
0.0068 4.ASD
0.9716 5.ADHD
0.6460 6.TS
0.0125 7.ANO
0.3330 8.OCD
FE summary
−0.3 −0.2 −0.1 0.0 0.1 0.2 0.3
PM−Plot
−log10(p)
0 5 10 15 20
0.0 0.2 0.4 0.6 0.8 1.0
D
rs10265001 (Meta P = 4.93 x 10−9)
Gene : MRPS33 , BRAF
GWAS P−value
0.0011 1.SCZ
1.31 x 10−7 2.BIP
0.0008 3.MD
0.0008 4.ASD
0.5910 5.ADHD
0.9701 6.TS
0.6232 7.ANO
0.0198 8.OCD
FE summary
−0.20 −0.15 −0.10 −0.05 0.00 0.05
Log odds ratio
PM−Plot
−log10(p)
0 5 10 15 20
0.0 0.2 0.4 0.6 0.8 1.0
m-value

Figure 3. Profile of disorder associations for illustrative pleiotropic loci: (A) rs8084351 on 18q21.2; (B) rs7193263 on 16p13.3; (C) rs117956829 on 11q14.3; and (D) rs10265001 on 7q34.

Within these 136 loci, multi-SNP-based conditional analysis (Yang et al., 2012) identified 10 additional SNPs with independent associations, resulting in a total of 146 independent lead SNPs (**Supplementary Table 4)**. To provide a quantitative estimate of the best fit configuration of cross-disorder genotype-phenotype relationships, we estimated the posterior probability of association (referred to as the *m-value)* with each disorder using a Bayesian statistical framework[17] (Online Methods; **Supplementary Table 5**). As recommended[17], an *m*-value threshold of 0.9 was used to predict with high confidence that a particular SNP was associated with a given disorder. Also, *m*-values of $\leq$ 0.1 were taken as strong evidence against association. Plots of the SNP *p*-value vs. *m*-value for all 146 lead SNPs are shown in **Supplementary Fig. 2**. Nearly 75% (N = 109/146) of the genome-wide significant SNPs were pleiotropic (i.e., associated with more than one disorder). As expected (**Supplementary Fig. 3**), configurations of disease association reflected the differences in the statistical power and genetic correlations between the samples. Of the 109 pleiotropic loci, 83% and 72% involved SCZ and BIP, respectively. MD, which had the largest case-control sample, was associated with 48% of the pleiotropic loci (N=52/109). Despite the relatively small sample size, ASD was implicated in 36% of the pleiotropic loci. Most of the ASD associations co-occurred with SCZ and BIP. The other disorders, ADHD, TS, OCD, and AN featured associations in 16%, 14%, 11%, and 7% of the pleiotropic loci, respectively. Of the single-disorder-specific loci, 81% and 16% were associated with SCZ and MD, respectively.

Table 2 summarizes 23 pleiotropic loci associated with at least four of the disorders. Among these loci, heterogeneity of effect sizes was minimal (*p*-value of Q > 0.1). Eleven of the 23 regions map to the intron of a protein-coding gene, and seven additional lead SNPs had at least one protein-coding gene within 100 kb. We used an array of functional genomics resources, including brain eQTL and Hi-C data to prioritize potential candidate genes to the identified regions (Online Methods; **Fig. 2b**). The Manhattan plot in **Fig. 2c** highlights the prioritized candidate genes.

Table 2. Summary of 23 loci with the broadest cross-disorder association

SNP	CHR	BP	A1	A2	candidateGene (evidence)	ADHD	ANO	ASD	BIP	MDD	OCD	SCZ	TS	mDisorder_0.9
rs10149470	14	104017953	A	G	-	0.961(1.05)	0.905(1.03)	0.97(1.03)	0.965(1.03)	1(1.03)	0.951(1.07)	1(1.05)	0.984(1.09)	8
rs10265001	7	140665521	C	G	-	0.924(0.96)	0.802(1)	0.984(0.96)	0.995(0.95)	1(0.97)	0.902(0.95)	0.901(0.98)	0.932(0.95)	7
rs11570190	11	57560452	A	C	CTNND1(g);OR5AK2(q);	0.908(0.96)	0.926(0.94)	0.992(0.94)	0.843(0.98)	1(0.96)	0.88(0.96)	0.929(0.97)	0.913(0.95)	6
rs11688767	2	57988194	A	T	BCL11A(h);	0.963(1.06)	0.165(0.91)	0.999(1.06)	0.972(1.04)	1(1.03)	0.574(0.98)	1(1.05)	0.963(1.08)	6
rs117956829	11	89339666	A	G	TRIM64B(ha);GRM5(hf),TRIM77(hf),TYR(hf);	0.905(1.03)	0.938(1.07)	0.976(1.04)	0.984(1.04)	0.993(1.02)	0.897(1.04)	1(1.07)	0.892(1.03)	6
rs12129573	1	73768366	A	C	-	0.987(0.92)	0.954(0.92)	0.992(0.95)	0.985(0.96)	1(0.96)	0.854(0.98)	1(0.94)	0.886(0.97)	6
rs12658451	5	103904037	T	C	-	0.74(0.99)	0.949(0.93)	0.963(0.97)	0.785(0.98)	1(0.96)	0.858(0.97)	0.973(0.97)	0.921(0.96)	5
rs1484144	4	80217597	T	C	-	0.97(1.07)	0.884(1.03)	0.973(1.03)	0.98(1.04)	1(1.02)	0.84(1.01)	0.998(1.04)	0.85(1.01)	5
rs1518367	2	198807015	A	T	PLCL1(g);SF3B1(q)	0.836(1.02)	0.827(1.02)	0.987(1.05)	0.93(1.03)	0.999(1.02)	0.917(1.07)	1(1.05)	0.729(0.99)	5
rs2332700	14	72417326	C	G	RGS6(g);	0.944(1.05)	0.855(1.02)	0.972(1.03)	0.877(1.02)	1(1.03)	0.853(1.02)	0.999(1.04)	0.963(1.07)	5
rs34215985	4	42047778	C	G	SLC30A9(g);SLC30A9(q);	0.927(0.95)	0.79(0.99)	0.97(0.96)	0.58(1)	1(0.98)	0.916(0.93)	1(0.95)	0.832(0.98)	5
rs5758265	22	41617897	A	G	L3MBTL2(g),CHADL(g);	0.723(1)	0.929(1.21)	0.972(1.1)	0.906(1.07)	1(1.07)	0.66(0.92)	0.997(1.11)	0.789(1.03)	5
rs6125656	20	48090779	A	G	KCNB1(g);	0.844(0.98)	0.833(0.99)	0.998(0.95)	0.979(0.97)	1(0.97)	0.868(0.98)	0.997(0.96)	0.97(0.93)	5
rs61867293	10	106563924	T	C	SORCS3(g);	0.929(1.05)	0.835(1.03)	0.894(1.03)	0.948(1.03)	1(1.04)	0.85(1.04)	1(1.07)	0.539(0.98)	4
rs6969410	7	110069015	T	G	-	0.845(0.98)	0.899(0.96)	0.929(0.97)	0.983(0.96)	1(0.97)	0.849(0.97)	1(0.93)	0.698(1)	4
rs7193263	16	6315880	A	G	RBFOX1(g);	0.897(0.96)	0.783(0.99)	0.913(0.97)	0.991(0.95)	1(0.97)	0.674(1.03)	1(0.94)	0.865(0.97)	4
rs7405404	16	13749859	T	C	-	0.716(0.99)	0.772(0.98)	0.986(0.95)	0.999(0.92)	0.783(0.98)	0.921(0.91)	0.988(0.96)	0.692(1)	4
rs7531118	1	72837239	T	C	-	0.865(1.04)	0.854(1.04)	0.966(1.05)	0.999(1.1)	1(1.04)	0.734(0.97)	0.999(1.07)	0.798(1.01)	4
rs78337797	12	23987925	T	G	SOX5(g);	0.849(1.03)	0.797(1)	0.97(1.06)	0.954(1.05)	1(1.04)	0.831(1.02)	0.996(1.06)	0.885(1.05)	4
rs79879286	7	24826589	C	G	-	0.755(1)	0.884(1.04)	0.951(1.03)	0.948(1.03)	0.999(1.03)	0.885(1.05)	1(1.08)	0.817(1.01)	4
rs8084351	18	50726559	A	G	DCC(g);DCC(q);	0.763(1.02)	0.765(1.02)	0.99(1.06)	0.939(1.04)	1(1.03)	0.726(1)	1(1.08)	0.562(0.98)	4
rs9360557	6	73132745	C	G	KCNQ5(ha);KCNQ5(hf),KCNQ5-IT1(hf);	0.768(1.01)	0.885(1.06)	0.986(1.06)	0.995(1.07)	0.985(1.02)	0.731(0.98)	0.999(1.07)	0.707(0.99)	4
rs9787523	10	106460460	T	C	SORCS3(g);	0.735(1)	0.885(1.04)	0.89(1.02)	0.885(1.02)	1(1.03)	0.913(1.07)	1(1.08)	0.978(1.09)	4

nearestGene: evidences for assigning index SNP to candidate genes were coded as: (g) genic SNP; (q) cis-eQTL target; (h) hi-C interacting gene based on FUMA; (hf) hi-C interacting in fetal brain based on Won et al. (2016); (ha) hi-C interac

Table 2: SNP ID, location, prioritized candidate gene, disorder-specific m-values and Odds ratios for 23 most pleiotropic loci. The number of disorders with high confidence association (mDisorder_0.9) is shown in the last column.

https://drive.google.com/open?id=18qFWLO7HdXf80zNqLBLJ4auXTrA101R8

Of the 109 risk loci with shared effects, the 18q21.2 region surrounding SNP rs8084351 at the netrin 1 receptor gene *DCC* featured the most pleiotropic association (P_{meta} = 4.26 x 10^{-12}; **Fig. 3a**). This region showed association with all eight psychiatric disorders, and has been previously associated with both MD and neuroticism (Wray et al. 2018; Turley et al. 2018 PMID 29292387). The product of *DCC* plays a key role in guiding axonal growth during neurodevelopment and serves as a master regulator of midline crossing and white matter projections (Bendriem, 2017). Gene expression data indicate that *DCC* expression peaks during early prenatal development (**Supplementary Fig. 4a**).

The second most pleiotropic locus in our analysis was identified in an intron of *RBFOX1* (RNA Binding Fox-1 Homolog 1) on 16p13.3 (lead SNP rs7193263; P_{meta} = 5.59 x 10^{-11}). The lead SNP showed association with all of the disorders except AN (**Fig. 3b**). *RBFOX1* (also called *A2BP1*) encodes a splicing regulator mainly expressed in neurons and known to target several genes important to neuronal development, including *NMDA* receptor 1 and voltage-gated calcium channels (Hamada N, 2015). Knock-down and silencing of *RBFOX1* during mouse corticogenesis impairs neuronal migration and synapse formation (Hamada N, 2015, 2016), implying its pivotal role in early cortical maturation. In contrast to *DCC*, however, developmental gene-expression of *RBFOX1* showed gradually increasing gene expression throughout the prenatal period (**Supplementary Fig. 4b**). Animal models and association studies have implicated *RBFOX1* in aggressive behaviors, a trait observed in several of the disorders in our analysis ('Fernandez-Castillo, 2017 #12870).

Of the 109 pleiotropic loci, 76 were identified in the GWAS of individual disorders, while the remaining 33 are novel. The most pleiotropic among these novel loci wasa region downstream of *NOX4* (NADPH Oxidase 4) that was associated with SCZ, BIP, MD, ASD, and AN (rs117956829; $P_{meta} = 1.82 \times 10^{-9}$; **Fig. 3c**). Brain Hi-C data (Won, 2016, Wang et al. Science) detected a direct interaction of the cross-disorder association region with *NOX4* in both adult and fetal brains (interaction $p=3.2\text{x}10^{-16}$ and $9.324\text{x}10^{-6}$, respectively). As a member of the family of *NOX* genes that encode subunits of *NADPH* oxidase, *NOX4* is a major source of superoxide production in human brain and a promoter of neural stem cell growth 'Topchiy, 2013 #12882} 'Kuroda, 2014 #12881}.

Figure 3d illustrates another novel psychiatric risk locus associated with SCZ, BIP, ASD, and OCD ($P_{meta} = 3.58 \times 10^{-8}$). The lead SNP rs10265001 resides between *MRPS33* (Mitochondrial Ribosomal Protein S33) and *BRAF* (B-Raf Proto-Oncogene, Serine/Threonine Kinase) on 7q34. The brain Hi-C data indicated interaction of the associated region with the promoters of two nearby genes: *BRAF*, which contributes to the MAP kinase signal transduction pathway and plays a role in postsynaptic responses of hippocampal neurons (Grantyn, 1973), and *KDM7A* (encoding Lysine Demethylase 7A), which plays a central role in the nervous system and midbrain development (Horton, 2010; Qi, 2010; Tsukada, 2010).

Our prior cross-disorder meta-analysis of five psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013) found no evidence of SNPs with antagonistic effects on two or more disorders. Here, we examined whether any variants with meta-analysis $p \leq 1\text{x}10^{-6}$ had opposite directional effects between disorders (Online Methods). After adjusting for having examined 206 loci across eight disorders ($q < 0.001$), we identified 11 loci with evidence of opposite directional effects on two or more disorders (**Fig. 4; Supplementary Table. 6**). The disorder configuration of opposite directional effects varied for the 11 loci, including three loci with opposite directional effects on SCZ and MD (rs301805, rs1933802, rs3806843), two loci between SCZ and ASD (rs9329221, rs2921036), and one locus (rs75595651) with opposite directional effects on the two mood disorders, BIP and MD. Notably, all of the six loci involving SCZ and BIP exhibited the same directional effect on the two disorders ($P_{binom} < 0.05$), in line with their strong genome-wide genetic correlation.

Figure 4. Eleven loci with opposite directional effects (could't include in the google doc) - Dotted circle indicates where disease-association is assumed (q<0.001).

https://www.dropbox.com/s/ro9bowc7756z9yd/Figure.4.antagonistic.pdf?dl=0

Functional characterization of pleiotropic risk loci

We conducted a series of bioinformatic analyses that examined whether loci with shared risk effects on multiple neuropsychiatric disorders had characteristic features that distinguished them from non-pleiotropic risk loci. First, we annotated the functional characteristics of 146 lead SNPs using various public data sources (Online Methods; **Supplementary Table 7-9**). Overall, they showed significant enrichment of genes expressed in the brain (*beta*=0.123, SE=0.0109, enrichment $p = 1.22 \times 10^{-29}$) and pituitary (*beta*=0.0916, SE=0.0136, $p = 8.74 \times 10^{-12}$), but not in the other Genotype-Tissue Expression (GTEx) tissues. (**Supplementary Table 10; Fig. 5a)**. A separate analysis of 109 pleiotropic risk loci also showed specific enrichment of genes expressed in multiple brain tissues ($p = 1.55 \times 10^{-5}$; **Supplementary Table 11**), while disorder-specific loci showed nominally enriched brain gene expression in the cortex ($p = 2.14 \times 10^{-2}$; **Supplementary Table 12**).

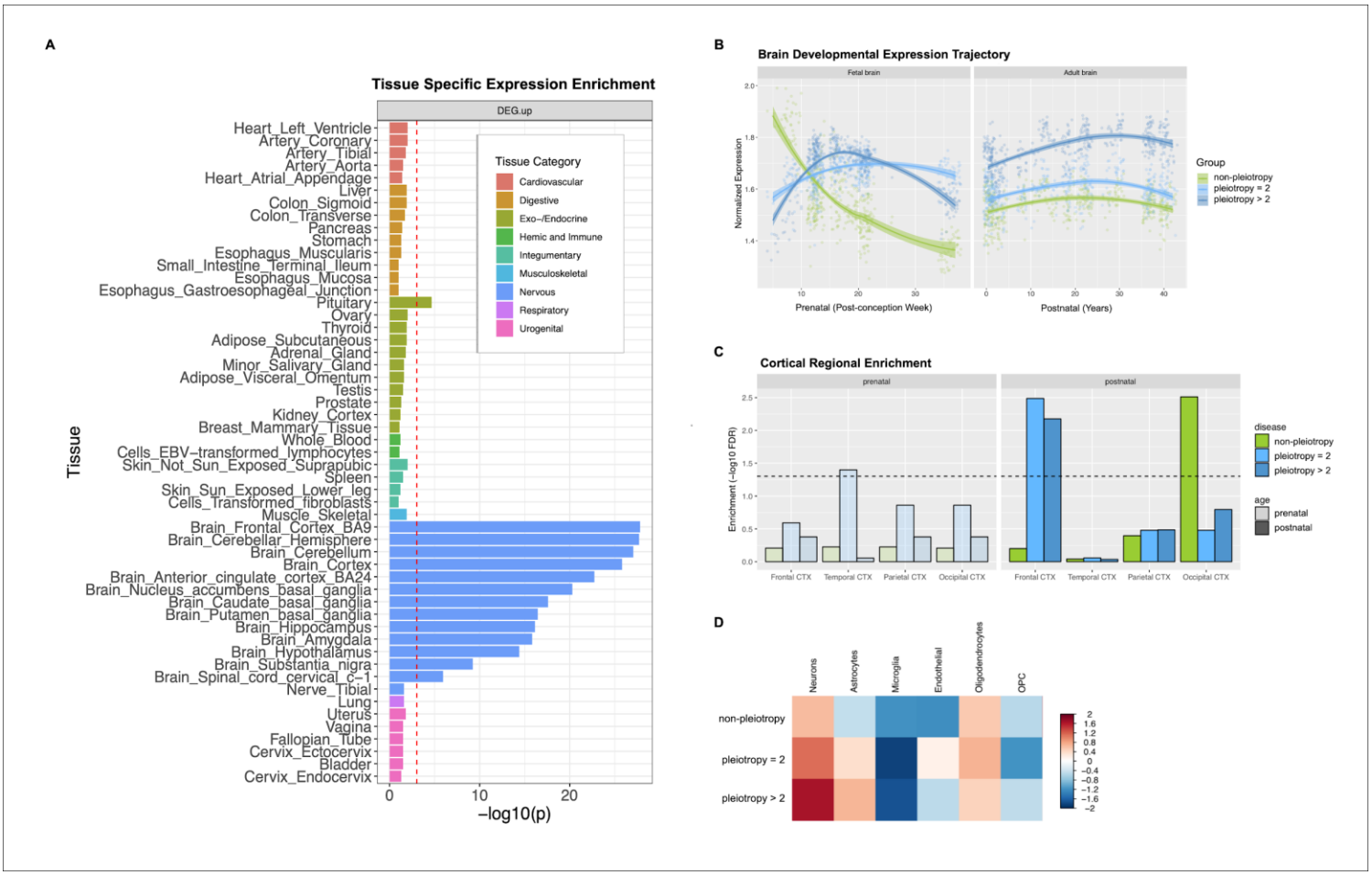


Figure 5. Results of functional genomics data analysis for pleiotropic vs. disorder-specific loci.

Gene-set enrichment analyses using Gene Ontology data suggested involvement of pleiotropic risk loci in neurodevelopmental processes (**Supplementary Table 13,14**). The 109 pleiotropic risk loci were enriched for genes involved in neurogenesis (gene-set enrichment $p = 9.67 \times 10^{-6}$), regulation of nervous system development ($p = 3.41 \times 10^{-5}$), and neuron differentiation ($p = 3.30 \times 10^{-5}$), while enrichment of these gene-sets was not seen for disorder-specific risk loci (adjusted enrichment $p > 0.05$). Pleiotropic risk loci also showed enrichment of genes involved in specific neurotransmitter-related pathways -- glutamate receptor signaling ($p = 2.45 \times 10^{-6}$) and voltage-gated calcium channel complex ($p = 5.72 \times 10^{-4}$) -- while non-pleiotropic risk loci, which were predominantly SCZ-associated, were over-represented among acetylcholine receptor genes ($p = 7.25 \times 10^{-8}$). Analysis of cortical gene expression data also suggested enrichment of pleiotropic risk genes in cortical glutamatergic neurons through layers 2-6 (**Supplementary Table 15**), further supporting the shared role of glutamate receptor signaling in the pathogenesis of diverse neuropsychiatric disorders.

In contrast to the differences in neuronal development and neuronal signaling pathways, pleiotropic and non-pleiotropic risk loci shared several characteristics related to genomic function. For instance, gene-set enrichment analyses indicated that both pleiotropic and non-pleiotropic risk loci were enriched for genes involved in the regulation of synaptic plasticity, neurotransmission, and synaptic cellular components.

More than 41% of the genes associated with our genome-wide significant loci, both pleiotropic and non-pleiotropic, were intolerant of loss of function mutations (pLI score ≥ 0.9); this is highly unlikely to occur by chance (Fisher's exact $p=4.90 \times 10^{-8}$). This finding was consistent when examining pleiotropic ($p=2.85 \times 10^{-11}$) and non-pleiotropic risk loci ($p=1.56 \times 10^{-3}$)separately.

Next, we compared spatio-temporal gene-expression patterns for the 109 pleiotropic risk loci and the 37 disorder-specific loci using post-mortem brain data. On average, disorder-specific and pleiotropic risk loci showed a similar level of gene expression in both prenatal and postnatal development after multiple testing correction (t-test $p > 0.025 \times 10^{-2}$; **Supplementary Fig. 5**). During prenatal development, non-pleiotropic loci (mainly SCZ-associated) showed peak expression in the first trimester, after which expression rapidly decreased, while pleiotropic genes associated with only 2 disorders ("*pleiotropy=2*"; 60 loci) and those associated with more than 2 ("*pleiotropy>2*", 49 loci)

showed peak expression around the second trimester (**Fig. 5b**). After birth, all three groups showed gradually increasing gene expression until adulthood. Expression levels were associated with the degree of pleiotropy, with the *pleiotropy>2* group showing higher gene expression than either the *pleiotropy=2* group (t-test $p < 2.10x10^{-4}$) or non-pleiotropic risk loci (t-test $p < 2.2x10^{-16}$).

Enrichment analyses using the genes preferentially expressed in specific cortical regions suggested that pleiotropic loci were over-represented among genes expressed in the frontal cortex, while non-pleiotropic loci were enriched in the occipital cortex (FDR $q<0.05$; **Fig. 5c**). Cell-type-specific analysis indicated that genes implicated in pleiotropic loci were mainly expressed in neurons (FDR $q<0.05$) but not in glial cell types. Further, enrichment of pleiotropic loci in neuronal cells was also associated with the degree of pleiotropy, as highlighted in **Fig. 5d**.

Previous studies of model organisms using gene knock-out experiments suggested that pleiotropic risk loci may undergo stronger selection than non-pleiotropic loci (Hill, 2012). However, we found no evidence that pleiotropic risk variants are under stronger evolutionary constraints (**Supplementary Table 16**). Various comparative genomics resources, including PhyloP (Pollard, 2010), PhastCons (Siepel, 2005), and GERP++ (Davydov, 2010), showed our top loci to have similar properties regardless of the extent of pleiotropy. Neither did we find differences between disorder-specific lead SNPs and pleiotropic SNPs with respect to their minor allele frequencies, average heterozygosity, or predicted allele ages (Kiezun, 2013). Pleiotropic and non-pleiotropic SNPs also did not differ in terms of the distance to nearest genes, distance to splicing sites, chromosome compositions, and predicted functional consequences of non-coding regulatory elements.

Relationship between cross-disorder genetic risk and other brain-related traits and diseases

To explore the genetic relationship of cross-disorder genetic risk with other traits, we treated this 8-disorder GWAS meta-analysis as a single “cross-disorder phenotype.” We applied LDSC to estimate SNP heritability (h^2_{SNP}) and genetic correlations with other phenotypes, using block jackknife-based standard errors to estimate statistical significance. The estimated h^2_{SNP} of the cross-disorder phenotype was 0.146 (SE 0.0058; observed scale). Using data for 28 brain-related traits selected from LDHub (Zheng et al., 2017), we found significant genetic correlations of the cross-disorder phenotype with seven traits (at a Bonferroni-corrected p-value threshold 0.002): never/ever smoking status, years of education, neuroticism, subjective well-being, and three sleep-related phenotypes (chronotype, insomnia, and excessive daytime sleepiness) (**Supplementary Table 17**).

GWAS catalog data for the 109 pleiotropic risk loci showed enrichment of implicated genes in a range of brain-related traits (**Supplementary Table 18**). As expected, the associated traits included previous studies of neuropsychiatric disorders including SCZ, BIP, and ASD. In addition, they were enriched among genes previously associated with neuroticism (corrected enrichment $p = 5.28 \times 10^{-6}$; *GRIK3, CTNND1, DRD2, RGS6, RBFOX1, ZNF804A, L3MBTL2, CHADL, RANGAP1, RSRC1, GRM3*) and cognitive ability (corrected $p = 7.15 \times 10^{-5}$; *PTPRF, NEGR1, ELOVL3, SORCS3, DCC, CACNA1I),* and night sleep phenotypes *(corrected* $p = 1.86 \times 10^{-2}$; *PBX1, NPAS3, RGS6, GRIN2A, MYO18A, TIAF1, CNTN4, PPP2R2B, TENM2, CSMD1*). We also found significant enrichment of pleiotropic risk genes in multiple measures of body mass index (BMI), supporting previous studies suggesting a shared etiologic basis between a range of neuropsychiatric disorders and obesity (Hartwig et al. 2016; Rajan and Menon 2017; Guenzel and Schober 2017).

DISCUSSION

In the largest cross-disorder GWAS meta-analysis of neuropsychiatric disorders to date, comprising more than 725,000 cases and controls across eight disorders, we identified 146 LD-independent lead SNPs associated with at least one disorder, including 35 novel loci. Of these, 109 loci were found to affect two or more disorders, although characterisation of this pleiotropy is partly dependent on per-disorder sample size. Our results provide four major insights into the shared genetic basis of psychiatric disorders.

First, modeling of genetic correlations among the eight disorders using two different methods (EFA and hierarchical clustering) identified three groups of disorders based on shared genomics: one comprising disorders characterized by compulsive behaviors (AN, OCD and TS), a second comprising mood and psychotic disorders (MD, BIP and SCZ), and a third comprising two early-onset neurodevelopmental disorders (ASD and ADHD) and one disorder each from the first two factors (TS and MD). The loading of MD on two factors may reflect biological heterogeneity within MD, consistent with recent evidence showing that early-onset depression is associated with genetic risk for ADHD and with neurodevelopmental phenotypes 'Rice, 2018 #12873}. Overall, these results indicate a substantial pairwise genetic correlation between multiple disorders along with a higher-level genetic structure that underlies psychopathology. These findings are at odds with the classical, categorical classification of mental illness.

Second, variant-level analyses support the existence of substantial pleiotropy, with nearly 75% of the 146 genome-wide significant SNPs influencing more than one of the eight examined disorders. We also identified a set of 23 loci with particularly extensive pleiotropic profiles, affecting four or more disorders. The most highly pleiotropic loc,us in our analyses, with evidence of association with all eight disorders, maps within *DCC,* a gene fundamental to the early development of white matter connections in the brain

(Bendriem and Ross, 2017). Prior studies showed that *DCC* is a master regulator of axon guidance (through its interactions with netrin-1 and draxin (Liu et al., 2018). Loss of function mutations in *DCC* cause severe neurodevelopmental syndromes involving loss of midline commissural tracts and diffuse disorganization of white matter tracts (Bendriem and Ross, 2017; Jamuar et al., 2017; Marsh et al., 2017). A highly pleiotropic effect of variation in *DCC* on diverse psychiatric disorders with childhood and adolescent onset would be consistent with its role in both early organization of neuronal circuits and the maturation of mesolimbic dopaminergic connections to the prefrontal cortex during adolescence (Hoops and Flores, 2017; Reynolds et al., 2018; Vosberg et al., 2018).

We also identified a set of loci that have opposite effects on risk of psychiatric disorders. Notably, these included loci with opposing effects on pairs of disorders that are genetically correlated and have common clinical features. For example, a SNP within *MRSA* was associated with opposing effects on two neurodevelopmental disorders (ASD and SCZ), and a variant within *KIAA1109* had opposite directional effects on major mood disorders (BIP and MD) (Table 3). These results underscore the complexity of genetic relationships among related disorders and suggest that overall genetic correlations may obscure antagonistic biological mechanisms that operate at the level of component loci and pathways as seen in immune-mediated diseases (Baurecht et al., 2015; Lettre and Rioux, 2008; Schmitt et al., 2016). This heterogeneity of effects between genetically correlated disorders is also consistent with a recent analysis that revealed loci contributing to biological differences between BIP and SCZ and found polygenic risk score associations with specific symptom dimensions (Bipolar et al., 2018).

Third, we found extensive evidence that neurodevelopmental effects underlie the cross-disorder genetics of mental illness. In addition to *DCC*, a link between pleiotropy and genetic effects on neurodevelopment was also seen for other top loci in our analysis, including *RBFOX1, BRAF*, and *KDM7A*, all of which have been shown in prior research to influence aspects of nervous system development. Gene enrichment analyses showed that pleiotropic loci were distinguished from disorder-specific loci by their involvement in neurodevelopmental pathways including neurogenesis, regulation of nervous system development, and neuron differentiation. These results are consistent with those of a smaller recent analysis in the population-based Danish iPSYCH cohort (comprising 46,008 cases and 19,526 controls across six neuropsychiatric disorders) (Schork et al., 2017). In that analysis, consistent with the present findings, functional genomic characterization of cross-disorder loci implicated fetal neurodevelopmental processes, with greater prenatal than postnatal expression. However, the specific loci, cell types, and pathways implicated in the iPSYCH analysis differed from those identified in our study. Of note, however, *SORCS3* emerged as a genome-wide significant cross-disorder locus in both studies.

Fourth, our analyses of spatiotemporal gene expression profiles revealed that pleiotropic loci are enriched among genes expressed in neuronal cell types, particularly in frontal or prefrontal regions. They also demonstrated a distinctive feature of genes related to pleiotropic loci: compared with disorder-specific loci, they are on average expressed at higher levels both prenatally and postnatally (Figure 4). More specifically, single-disorder (mainly SCZ) loci were related to genes that were preferentially expressed in the first fetal trimester followed by a decline over the prenatal period and then relatively stable levels postnatally. In contrast, expression of genes related to pleiotropic loci peaked in the second trimester and remained overexpressed throughout the lifespan. When dividing the pleiotropic loci into bins of those associated with two disorders (mainly SCZ and BIP) vs. three or more disorders, we observed a consistent gradient of greater expression associated with broader pleiotropy.

Taken together, our results suggest that pleiotropic loci appear to be distinguished by both their differential importance in neurodevelopmental processes and their heightened brain expression after the first trimester. Apart from this, however, pleiotropic loci were similar to non-pleiotropic loci across a range of other functional features, including intolerance to loss-of-function mutations, evidence of selection, minor allele frequencies, and genomic position relative to functional elements.

Overall, our results identify a range of pleiotropic effects among loci associated with psychiatric disorders. Consistent with prior research (Brainstorm et al., 2018) (Cross-Disorder Group of the Psychiatric Genomics et al., 2013), we found substantial pairwise genetic correlations across child- and adult-onset disorders and extended these findings by demonstrating clusters of genetically-related disorders. These results augment a substantial body of research demonstrating that genetic influences on psychopathology do not map cleanly onto the clinical nosology instantiated in the DSM or ICD (Smoller et al., 2018). Using a range of bioinformatic and functional genomic analyses, we find that loci with pleiotropic effects are distinguished by their involvement in early neurodevelopment and increased expression beginning in the second trimester of fetal development and persisting throughout adulthood. Taken together, the analyses presented here suggest that genetic influences on psychiatric disorders comprise at least two general classes of loci. The first comprises a set of genes that confer relatively broad liability to psychiatric disorders by acting on early neurodevelopment and the establishment of brain circuitry. These pleiotropic genes begin to come online by the second trimester of fetal development and exhibit differentially high expression thereafter. Such loci may underlie a latent general psychopathology factor (the “p” factor) (Caspi et al., 2014) that has been identified in developmental studies of mental disorders, comprising transdiagnostic symptom clusters (internalizing, externalizing, and psychotic) (Caspi et al., 2014). The expression and differentiation of this generalized genetic risk into discrete psychiatric syndromes (e.g., ASD, BIP, AN) may then involve

direct and/or interactive effects of additional sets of loci and environmental factors, possibly mediated by epigenetic effects, that shape phenotypic expression via effects on brain structure/function and behavior. Further research will be needed to clarify the nature of such effects.

Our results should be interpreted in light of several limitations. First, while our dataset is the largest genome-wide cross-disorder analysis to date, data available for individual disorders varied substantially—from a minimum of 9725 cases and controls for OCD to 461,134 cases and controls for MD. This imbalance of sample size may have limited our power to detect pleiotropic effects on underrepresented disorders. Second, it is possible that comorbidity among disorders contributed to apparent pleiotropy; however we found that less than 2% of cases overlapped between disorder datasets (excluding 23andMe data) and we adjusted for overlap in meta-analysis. Second, the method we applied to detect cross-phenotype association, which combines an all-subsets fixed-effects GWAS meta-analysis with a Bayesian method for evaluating the best-fit configuration of genotype-phenotype associations, is one of several approaches (Solovieff et al., 2013). However, we have previously shown that this method outperforms a range of alternatives for detecting pleiotropy. (Zhu et al., 2018) Third, our designation of loci as pleiotropic vs. non-pleiotropic loci refers only to their observed effects on the eight target brain disorders. Thus, some of the “non-pleiotropic” loci may have additional effects on psychiatric phenotypes that were not included in our meta-analysis and/or on non-psychiatric phenotypes. Fourth, our functional genomic analyses were constrained by the limitations of existing resources (e.g. spatiotemporal gene expression data resources). Our work underscores the need for more comprehensive functional data including single cell transcriptomic and epigenomic profiles across development and brain tissues. Fifth, we included only individuals of European ancestry to avoid potential confounding due to ancestral heterogeneity across distinct disorder studies. Similar efforts are needed to examine these questions in other populations.

In sum, in a large-scale cross-disorder genome-wide meta-analysis, we identified three genetic factors underlying the genetic basis of eight psychiatric disorders. We also identified 109 genomic loci with pleiotropic effects, of which 33 have not previously been associated with any of the individual disorders. In addition, we identified 11 loci with opposing directional effects on two or more psychiatric disorders. These results highlight disparities between our clinically-defined classification of psychiatric disorders and underlying biology. Finally, we found that genes associated with multiple psychiatric disorders are disproportionately associated with biological pathways related to neurodevelopment and exhibit distinctive gene expression patterns, with enhanced expression beginning in the second prenatal trimester and persistently elevated expression relative to less pleiotropic genes. Therapeutic modulation of pleiotropic gene products could have broad-spectrum effects on psychopathology.

STAR* METHODS

(link to this file: https://drive.google.com/open?id=1r7Nl4Kt4pg0rzoqfkAgbKAlfExcj9s0v)
Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- CONTACT FOR REAGENT AND RESOURCE SHARING
- EXPERIMENTAL MODEL AND SUBJECT DETAILS
  - Genotyped sample description
  - Genotype quality control, imputation, and association analysis
- QUANTIFICATION AND STATISTICAL ANALYSIS
  - Genome-wide SNP-heritability estimation
  - Factor analysis and genomic SEM
  - Summary-data-based meta-analysis
  - Disease-association modeling
  - Candidate-gene mapping
  -
- DATA AND SOFTWARE AVAILABILITY

SUPPLEMENTAL INFORMATION

Supplemental Information includes 5 figures, 18 tables, and a list of consortium author affiliations and can be found with this article online at XXX.

CONSORTIA

Cell format: All consortia author names without affiliation information
Note: 23andme will be included as author, here.

ACKNOWLEDGMENTS

Full acknowledgments and a list of funding are in the Supplementary Note. The work of the contributing groups was supported by numerous grants from governmental and charitable bodies as well as philanthropic donation. Specifically, P.H.L. (R00MH101367), …, J.W.S. (R01MH106547; R01MH117599; U01HG008685). We thank the research participants and employees of 23andMe, Inc. for their contribution to this study.

AUTHOR CONTRIBUTIONS

Writing Group: P.H.L, Y.A.F., V.A., S.V.F., B.M.N., K.S.M., L.T., S.R., N.W., M.N., G.B., J.W., J.S., H.E., J.G., O.A., M.B.S., C.A.M., A.F., S.S., M.M., A.Z., A.B., K.S.K., J.W.S.

(Chair). *Analysis Group*: P.H.L., H.W., Y.A.F, D.H.G., J.R, V.A., A.D.G, E.T-D., M.G.N., and Z.Z., D.P. Disorder-specific data collection, analysis, and identification of duplicate subjects were conducted by S.R., E.S., R.A., D.Y., R.W., D.M., M.M., A.B., 23andme, and L.E.D. *Editorial Revisions Group*: J.I.N., others TBD The remaining authors contributed to the recruitment, genotyping, or data processing for the contributing components of the study. All other authors saw, had the opportunity to comment on, and approved the final draft.

DECLARATION OF INTERESTS

J.W.S. is an unpaid member of the Bipolar/Depression Research Community Advisory Panel of 23andMe. The other authors declare no competing interests. ⇒ Need to be checked

HRK (Henry R. Kranzler) is a member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, which was supported in the last three years by AbbVie, Alkermes, Ethypharm, Indivior, Lilly, Lundbeck, Otsuka, Pfizer, Arbor, and Amygdala Neurosciences. HRK and JG (Joel Gelernter) are named as inventors on PCT patent application #15/878,640 entitled: "Genotype-guided dosing of opioid agonists," filed January 24, 2018.

BMN (Benjamin M Neale) is a member of the Deep Genomics Scientific Advisory Board, a consultant for Camp4 Therapeutics Corporation, a consultant for Merck & Co., a consultant for Avanir Pharmaceuticals, Inc, and a consultant for Takeda Pharmaceutical.

KMV (Kirsten Müller-Vahl) has nonfinancial competing interests as a member of the TAA medical advisory board, the scientific advisory board of the German Tourette Association TGD, the board of directors of the German (ACM) and the International (IACM) Association for Cannabinoid Medicines, and the committee of experts for narcotic drugs at the federal opium bureau of the Federal Institute for Drugs and Medical Devices (BfArM) in Germany; has received financial or material research support from the EU (FP7-HEALTH-2011 No. 278367, FP7-PEOPLE-2012-ITN No. 316978), the German Research Foundation (DFG: GZ MU 1527/3-1), the German Ministry of Education and Research (BMBF: 01KG1421), the National Institute of Mental Health (NIMH), the Tourette Gesellschaft Deutschland e.V., the Else-Kroner-Fresenius-Stiftung, and GW, Almirall, Abide Therapeutics, and Therapix Biosiences; has served as a guest editor for Frontiers in Neurology on the research topic "The neurobiology and genetics of Gilles de la Tourette syndrome: new avenues through large-scale collaborative projects", is an associate editor for "Cannabis and Cannabinoid Research" and an Editorial Board Member of "Medical Cannabis and Cannabinoids"; has received consultant's honoraria from Abide Therapeutics, Fundacion Canna, Therapix Biosiences

and Wayland Group, speaker's fees from Tilray, and royalties from Medizinisch Wissenschaftliche Verlagsgesellschaft Berlin, and is a consultant for Zynerba Pharmaceuticals.

JIN has been an investigator for Assurex and is currently an investigator for Janssen.

BF has received educational speaking fees from Medice and Shire.

REFERENCES

Bansal, V., Mitjans M, Burik CAP, Linnér RK, Okbay A, Rietveld CA, Begemann M, Bonn S, Ripke S, de Vlaming R, Nivard MG, Ehrenreich H, Koellinger PD (2018). Genome-wide association study results for educational attainment aid in identifying genetic heterogeneity of schizophrenia. Nat Commun *9*, 3078.

Barban, N., Jansen, R., de Vlaming, R., Vaez, A., Mandemakers, J.J., Tropf, F.C., Shen, X., Wilson, J.F., Chasman, D.I., Nolte, I.M.*, et al.* (2016). Genome-wide analysis identifies 12 loci influencing human reproductive behavior. Nat Genet *48*, 1462-1472.

Bendriem, R., Ross ME. (2017). Wiring the Human Brain: A User's Handbook. Neuron *95*, 482-485.

Berndt, S.I., Gustafsson, S., Magi, R., Ganna, A., Wheeler, E., Feitosa, M.F., Justice, A.E., Monda, K.L., Croteau-Chonka, D.C., Day, F.R.*, et al.* (2013). Genome-wide meta-analysis identifies 11 new loci for anthropometric traits and provides insights into genetic architecture. Nat Genet *45*, 501-512.

Bhattacharjee, S., Rajaraman, P., Jacobs, K.B., Wheeler, W.A., Melin, B.S., Hartge, P., GliomaScan, C., Yeager, M., Chung, C.C., Chanock, S.J.*, et al.* (2012). A subset-based approach improves power and interpretation for the combined analysis of genetic association studies of heterogeneous traits. American journal of human genetics *90*, 821-835.

Brainstorm Consortium, A.V., Bulik-Sullivan B, Finucane HK, Walters RK, Bras J, Duncan L, Escott-Price V, Falcone GJ, Gormley P, Malik R, Patsopoulos NA, Ripke S, Wei Z, Yu D, Lee PH, Turley P, Grenier-Boley B, Chouraki V, Kamatani Y, Berr C, Letenneur L, Hannequin D, Amouyel P, Boland A, Deleuze JF, Duron E, Vardarajan BN, Reitz C, Goate AM, Huentelman MJ, Kamboh MI, Larson EB, Rogaeva E, St George-Hyslop P, Hakonarson H, Kukull WA, Farrer LA, Barnes LL, Beach TG, Demirci FY, Head E, Hulette CM, Jicha GA, Kauwe JSK, Kaye JA, Leverenz JB, Levey AI, Lieberman AP, Pankratz VS, Poon WW, Quinn JF, Saykin AJ, Schneider LS, Smith AG, Sonnen JA, Stern RA, Van Deerlin VM, Van Eldik LJ, Harold D, Russo G, Rubinsztein DC, Bayer A, Tsolaki M, Proitsi P, Fox NC, Hampel H, Owen MJ, Mead S, Passmore P, Morgan K, Nöthen MM, Rossor M, Lupton MK, Hoffmann P, Kornhuber J, Lawlor B, McQuillin A, Al-Chalabi A, Bis JC, Ruiz A, Boada M, Seshadri S, Beiser A, Rice K, van der Lee SJ, De Jager PL, Geschwind DH, Riemenschneider M, Riedel-Heller S, Rotter JI, Ransmayr G, Hyman BT, Cruchaga C, Alegret M, Winsvold B, Palta P, Farh KH, Cuenca-Leon E, Furlotte N, Kurth T, Ligthart L, Terwindt GM, Freilinger T, Ran C, Gordon SD, Borck G, Adams HHH, Lehtimäki T, Wedenoja J, Buring JE, Schürks M, Hrafnsdottir M, Hottenga JJ, Penninx B, Artto V, Kaunisto M, Vepsäläinen S, Martin NG, Montgomery GW, Kurki MI, Hämäläinen E, Huang H, Huang J, Sandor C, Webber C, Muller-Myhsok B, Schreiber S, Salomaa V, Loehrer E, Göbel H, Macaya A, Pozo-Rosich P, Hansen T, Werge T, Kaprio J, Metspalu A, Kubisch C, Ferrari MD, Belin AC, van den Maagdenberg AMJM, Zwart JA, Boomsma D, Eriksson N, Olesen J, Chasman DI, Nyholt DR, Avbersek A, Baum L, Berkovic S, Bradfield J, Buono R, Catarino CB, Cossette P, De Jonghe P, Depondt C, Dlugos D, Ferraro TN, French J, Hjalgrim H, Jamnadas-Khoda J, Kälviäinen R, Kunz WS, Lerche H, Leu C, Lindhout D, Lo W, Lowenstein D, McCormack M, Møller RS, Molloy A, Ng PW, Oliver K, Privitera M, Radtke R, Ruppert AK, Sander T, Schachter S, Schankin C, Scheffer I, Schoch S, Sisodiya SM, Smith P, Sperling M, Striano P, Surges R, Thomas GN, Visscher F, Whelan CD, Zara F, Heinzen EL, Marson A, Becker F, Stroink H, Zimprich F, Gasser T, Gibbs R, Heutink P, Martinez M, Morris HR, Sharma M, Ryten M, Mok KY, Pulit S, Bevan S, Holliday E, Attia J, Battey T, Boncoraglio G, Thijs V, Chen WM, Mitchell B, Rothwell P, Sharma P, Sudlow C, Vicente A, Markus H, Kourkoulis C, Pera J, Raffeld M, Silliman S, Boraska Perica V, Thornton LM, Huckins LM, William Rayner N, Lewis CM, Gratacos M, Rybakowski F, Keski-Rahkonen A, Raevuori A, Hudson JI, Reichborn-Kjennerud T, Monteleone P, Karwautz A, Mannik K, Baker JH, O'Toole JK, Trace SE, Davis OSP, Helder SG, Ehrlich S, Herpertz-Dahlmann B, Danner UN, van Elburg AA, Clementi M, Forzan M, Docampo E, Lissowska J, Hauser J, Tortorella A, Maj M, Gonidakis F, Tziouvas K, Papezova H, Yilmaz Z, Wagner G, Cohen-Woods S, Herms S, Julià A, Rabionet R, Dick DM, Ripatti S, Andreassen

OA, Espeseth T, Lundervold AJ, Steen VM, Pinto D, Scherer SW, Aschauer H, Schosser A, Alfredsson L, Padyukov L, Halmi KA, Mitchell J, Strober M, Bergen AW, Kaye W, Szatkiewicz JP, Cormand B, Ramos-Quiroga JA, Sánchez-Mora C, Ribasés M, Casas M, Hervas A, Arranz MJ, Haavik J, Zayats T, Johansson S, Williams N, Dempfle A, Rothenberger A, Kuntsi J, Oades RD, Banaschewski T, Franke B, Buitelaar JK, Arias Vasquez A, Doyle AE, Reif A, Lesch KP, Freitag C, Rivero O, Palmason H, Romanos M, Langley K, Rietschel M, Witt SH, Dalsgaard S, Børglum AD, Waldman I, Wilmot B, Molly N, Bau CHD, Crosbie J, Schachar R, Loo SK, McGough JJ, Grevet EH, Medland SE, Robinson E, Weiss LA, Bacchelli E, Bailey A, Bal V, Battaglia A, Betancur C, Bolton P, Cantor R, Celestino-Soper P, Dawson G, De Rubeis S, Duque F, Green A, Klauck SM, Leboyer M, Levitt P, Maestrini E, Mane S, De-Luca DM, Parr J, Regan R, Reichenberg A, Sandin S, Vorstman J, Wassink T, Wijsman E, Cook E, Santangelo S, Delorme R, Rogé B, Magalhaes T, Arking D, Schulze TG, Thompson RC, Strohmaier J, Matthews K, Melle I, Morris D, Blackwood D, McIntosh A, Bergen SE, Schalling M, Jamain S, Maaser A, Fischer SB, Reinbold CS, Fullerton JM, Guzman-Parra J, Mayoral F, Schofield PR, Cichon S, Mühleisen TW, Degenhardt F, Schumacher J, Bauer M, Mitchell PB, Gershon ES, Rice J, Potash JB, Zandi PP, Craddock N, Ferrier IN, Alda M, Rouleau GA, Turecki G, Ophoff R, Pato C, Anjorin A, Stahl E, Leber M, Czerski PM, Cruceanu C, Jones IR, Posthuma D, Andlauer TFM, Forstner AJ, Streit F, Baune BT, Air T, Sinnamon G, Wray NR, MacIntyre DJ, Porteous D, Homuth G, Rivera M, Grove J, Middeldorp CM, Hickie I, Pergadia M, Mehta D, Smit JH, Jansen R, de Geus E, Dunn E, Li QS, Nauck M, Schoevers RA, Beekman AT, Knowles JA, Viktorin A, Arnold P, Barr CL, Bedoya-Berrio G, Bienvenu OJ, Brentani H, Burton C, Camarena B, Cappi C, Cath D, Cavallini M, Cusi D, Darrow S, Denys D, Derks EM, Dietrich A, Fernandez T, Figee M, Freimer N, Gerber G, Grados M, Greenberg E, Hanna GL, Hartmann A, Hirschtritt ME, Hoekstra PJ, Huang A, Huyser C, Illmann C, Jenike M, Kuperman S, Leventhal B, Lochner C, Lyon GJ, Macciardi F, Madruga-Garrido M, Malaty IA, Maras A, McGrath L, Miguel EC, Mir P, Nestadt G, Nicolini H, Okun MS, Pakstis A, Paschou P, Piacentini J, Pittenger C, Plessen K, Ramensky V, Ramos EM, Reus V, Richter MA, Riddle MA, Robertson MM, Roessner V, Rosário M, Samuels JF, Sandor P, Stein DJ, Tsetsos F, Van Nieuwerburgh F, Weatherall S, Wendland JR, Wolanczyk T, Worbe Y, Zai G, Goes FS, McLaughlin N, Nestadt PS, Grabe HJ, Depienne C, Konkashbaev A, Lanzagorta N, Valencia-Duarte A, Bramon E, Buccola N, Cahn W, Cairns M, Chong SA, Cohen D, Crespo-Facorro B, Crowley J, Davidson M, DeLisi L, Dinan T, Donohoe G, Drapeau E, Duan J, Haan L, Hougaard D, Karachanak-Yankova S, Khrunin A, Klovins J, Kučinskas V, Lee Chee Keong J, Limborska S, Loughland C, Lönnqvist J, Maher B, Mattheisen M, McDonald C, Murphy KC, Nenadic I, van Os J, Pantelis C, Pato M, Petryshen T, Quested D, Roussos P, Sanders AR, Schall U, Schwab SG, Sim K, So HC, Stögmann E, Subramaniam M, Toncheva D, Waddington J, Walters J, Weiser M, Cheng W, Cloninger R, Curtis D, Gejman PV, Henskens F, Mattingsdal M, Oh SY, Scott R, Webb B, Breen G, Churchhouse C, Bulik CM, Daly M, Dichgans M, Faraone SV, Guerreiro R, Holmans P, Kendler KS, Koeleman B, Mathews CA, Price A, Scharf J, Sklar P, Williams J, Wood NW, Cotsapas C, Palotie A, Smoller JW, Sullivan P, Rosand J, Corvin A, Neale BM, Schott JM, Anney R, Elia J, Grigoroiu-Serbanescu M, Edenberg HJ, Murray R. (2018). Analysis of shared heritability in common disorders of the brain. Science *360*, eaap8757.

Bulik-Sullivan, B., Finucane, H.K., Anttila, V., Gusev, A., Day, F.R., Loh, P.R., ReproGen, C., Psychiatric Genomics, C., Genetic Consortium for Anorexia Nervosa of the Wellcome Trust Case Control, C., Duncan, L.*, et al.* (2015a). An atlas of genetic correlations across human diseases and traits. Nat Genet *47*, 1236-1241.

Bulik-Sullivan, B., Loh PR, Finucane HK, Ripke S, Yang J; Schizophrenia Working Group of the Psychiatric Genomics Consortium, Patterson N, Daly MJ, Price AL, Neale BM. (2015). LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet *47*, 291-295.

Bulik-Sullivan, B.K., Loh, P.R., Finucane, H.K., Ripke, S., Yang, J., Schizophrenia Working Group of the Psychiatric Genomics, C., Patterson, N., Daly, M.J., Price, A.L., and Neale, B.M. (2015b). LD Score

regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet *47*, 291-295.

Cross Disorder Group of the Psychiatric Genomics Consoritum, Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, Perlis RH, Mowry BJ, Thapar A, Goddard ME, Witte JS, Absher D, Agartz I, Akil H, Amin F, Andreassen OA, Anjorin A, Anney R, Anttila V, Arking DE, Asherson P, Azevedo MH, Backlund L, Badner JA, Bailey AJ, Banaschewski T, Barchas JD, Barnes MR, Barrett TB, Bass N, Battaglia A, Bauer M, Bayés M, Bellivier F, Bergen SE, Berrettini W, Betancur C, Bettecken T, Biederman J, Binder EB, Black DW, Blackwood DH, Bloss CS, Boehnke M, Boomsma DI, Breen G, Breuer R, Bruggeman R, Cormican P, Buccola NG, Buitelaar JK, Bunney WE, Buxbaum JD, Byerley WF, Byrne EM, Caesar S, Cahn W, Cantor RM, Casas M, Chakravarti A, Chambert K, Choudhury K, Cichon S, Cloninger CR, Collier DA, Cook EH, Coon H, Cormand B, Corvin A, Coryell WH, Craig DW, Craig IW, Crosbie J, Cuccaro ML, Curtis D, Czamara D, Datta S, Dawson G, Day R, De Geus EJ, Degenhardt F, Djurovic S, Donohoe GJ, Doyle AE, Duan J, Dudbridge F, Duketis E, Ebstein RP, Edenberg HJ, Elia J, Ennis S, Etain B, Fanous A, Farmer AE, Ferrier IN, Flickinger M, Fombonne E, Foroud T, Frank J, Franke B, Fraser C, Freedman R, Freimer NB, Freitag CM, Friedl M, Frisén L, Gallagher L, Gejman PV, Georgieva L, Gershon ES, Geschwind DH, Giegling I, Gill M, Gordon SD, Gordon-Smith K, Green EK, Greenwood TA, Grice DE, Gross M, Grozeva D, Guan W, Gurling H, De Haan L, Haines JL, Hakonarson H, Hallmayer J, Hamilton SP, Hamshere ML, Hansen TF, Hartmann AM, Hautzinger M, Heath AC, Henders AK, Herms S, Hickie IB, Hipolito M, Hoefels S, Holmans PA, Holsboer F, Hoogendijk WJ, Hottenga JJ, Hultman CM, Hus V, Ingason A, Ising M, Jamain S, Jones EG, Jones I, Jones L, Tzeng JY, Kähler AK, Kahn RS, Kandaswamy R, Keller MC, Kennedy JL, Kenny E, Kent L, Kim Y, Kirov GK, Klauck SM, Klei L, Knowles JA, Kohli MA, Koller DL, Konte B, Korszun A, Krabbendam L, Krasucki R, Kuntsi J, Kwan P, Landén M, Långström N, Lathrop M, Lawrence J, Lawson WB, Leboyer M, Ledbetter DH, Lee PH, Lencz T, Lesch KP, Levinson DF, Lewis CM, Li J, Lichtenstein P, Lieberman JA, Lin DY, Linszen DH, Liu C, Lohoff FW, Loo SK, Lord C, Lowe JK, Lucae S, MacIntyre DJ, Madden PA, Maestrini E, Magnusson PK, Mahon PB, Maier W, Malhotra AK, Mane SM, Martin CL, Martin NG, Mattheisen M, Matthews K, Mattingsdal M, McCarroll SA, McGhee KA, McGough JJ, McGrath PJ, McGuffin P, McInnis MG, McIntosh A, McKinney R, McLean AW, McMahon FJ, McMahon WM, McQuillin A, Medeiros H, Medland SE, Meier S, Melle I, Meng F, Meyer J, Middeldorp CM, Middleton L, Milanova V, Miranda A, Monaco AP, Montgomery GW, Moran JL, Moreno-De-Luca D, Morken G, Morris DW, Morrow EM, Moskvina V, Muglia P, Mühleisen TW, Muir WJ, Müller-Myhsok B, Murtha M, Myers RM, Myin-Germeys I, Neale MC, Nelson SF, Nievergelt CM, Nikolov I, Nimgaonkar V, Nolen WA, Nöthen MM, Nurnberger JI, Nwulia EA, Nyholt DR, O'Dushlaine C, Oades RD, Olincy A, Oliveira G, Olsen L, Ophoff RA, Osby U, Owen MJ, Palotie A, Parr JR, Paterson AD, Pato CN, Pato MT, Penninx BW, Pergadia ML, Pericak-Vance MA, Pickard BS, Pimm J, Piven J, Posthuma D, Potash JB, Poustka F, Propping P, Puri V, Quested DJ, Quinn EM, Ramos-Quiroga JA, Rasmussen HB, Raychaudhuri S, Rehnström K, Reif A, Ribasés M, Rice JP, Rietschel M, Roeder K, Roeyers H, Rossin L, Rothenberger A, Rouleau G, Ruderfer D, Rujescu D, Sanders AR, Sanders SJ, Santangelo SL, Sergeant JA, Schachar R, Schalling M, Schatzberg AF, Scheftner WA, Schellenberg GD, Scherer SW, Schork NJ, Schulze TG, Schumacher J, Schwarz M, Scolnick E, Scott LJ, Shi J, Shilling PD, Shyn SI, Silverman JM, Slager SL, Smalley SL, Smit JH, Smith EN, Sonuga-Barke EJ, St Clair D, State M, Steffens M, Steinhausen HC, Strauss JS, Strohmaier J, Stroup TS, Sutcliffe JS, Szatmari P, Szelinger S, Thirumalai S, Thompson RC, Todorov AA, Tozzi F, Treutlein J, Uhr M, van den Oord EJ, Van Grootheest G, Van Os J, Vicente AM, Vieland VJ, Vincent JB, Visscher PM, Walsh CA, Wassink TH, Watson SJ, Weissman MM, Werge T, Wienker TF, Wijsman EM, Willemsen G, Williams N, Willsey AJ, Witt SH, Xu W, Young AH, Yu TW, Zammit S, Zandi PP, Zhang P, Zitman FG, Zöllner S; International Inflammatory Bowel Disease Genetics Consortium (IIBDGC), Devlin B, Kelsoe JR, Sklar P, Daly MJ, O'Donovan MC, Craddock N, Sullivan PF, Smoller JW, Kendler KS, Wray NR. (2013). Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat Genet *45*, 984-994.

Cross-Disorder Group of the Psychiatric Genomics Consortium, Smoller JW, Ripke S, Lee PH, Neale B, Nurnberger JI, Santangelo S, Sullivan PF, Perlis RH, Purcell SM, Fanous A, Neale MC, Rietschel M, Schulze TG, Thapar A, Anney R, Buitelaar JK, Farone SV, Hoogendijk WJ, Levinson DF, Lesch KP, Riley B, Schachar R, Sonuga-Barke E, Absher D, Agartz I, Akil H, Amin F, Andreassen OA, Anjorin A, Arking D, Asherson P, Azevedo MH, Backlund L, Badner JA, Banaschewski T, Barchas JD, Barnes MR, Bass N, Bauer M, Bellivier F, Bergen SE, Berrettini W, Bettecken T, Biederman J, Binder EB, Black DW, Blackwood DH, Bloss CS, Boehnke M, Boomsma DI, Breen G, Breuer R, Buccola NG, Bunner WE, Burmeister M, Buxbaum JD, Byerley WF, Sian C, Cantor RM, Chakravarti A, Chambert K, Chicon S, Cloniger CR, Collier DA, Cook E, Coon H, Corvin A, Coryell WH, Craig DW, Craig IW, Curtis D, Czamara D, Daly M, Datta S, Day R, De Geus EJ, Degenhardt F, Devlin B, Srdjan D, Doyle AE, Duan J, Dudbridge F, Edenberg HJ, Elkin A, Etain B, Farmer AE, Ferreira MA, Ferrier IN, Flickinger M, Foroud T, Frank J, Franke B, Fraser C, Freedman R, Freimer NB, Friedl M, Frisén L, Gejman PV, Georgieva L, Gershon ES, Giegling I, Gill M, Gordon SD, Gordon-Smith K, Green EK, Greenwood TA, Gross M, Grozeva D, Guan W, Gurling H, Gustafsson Ó, Hakonarson H, Hamilton SP, Hamshere ML, Hansen TF, Hartmann AM, Hautzinger M, Heath AC, Henders AK, Herms S, Hickie IB, Hipolito M, Hoefels S, Holmans PA, Holsboer F, Hottenga JJ, Hultman CM, Ingason A, Ising M, Jamain S, Jones EG, Jones L, Jones I, Jung-Ying T, Kahler A, Kandaswamy R, Keller MC, Kelsoe JR, Kennedy JL, Kenny E, Kim Y, Kirov GK, Knowles JA, Kohli MA, Koller DL, Konte B, Korszun A, Krasucki R, Kuntsi J, Phoenix K, Landén M, Langstrom N, Lathrop M, Lawrence J, Lawson WB, Leboyer M, Lencz T, Lesch KP, Lewis CM, Li J, Lichtenstein P, Lieberman JA, Lin D, Liu C, Lohoff FW, Loo SK, Lucae S, MacIntyre D, Madden PA, Magnusson P, Mahon PB, Maier W, Malhotra AK, Mattheisen M, Matthews K, Mattingsdal M, McCarroll S, McGhee KA, McGough JJ, McGrath PJ, McGuffin P, McInnis MG, McIntosh A, McKinney R, McClean AW, McMahon FJ, McQuillin A, Medeiros H, Medland SE, Meier S, Melle I, Meng F, Middeldorp CM, Middleton L, Vihra M, Mitchell PB, Montgomery GW, Moran J, Morken G, Morris DW, Moskvina V, Mowry BJ, Muglia P, Mühleisen TW, Muir WJ, Müller-Myhsok B, Myers RM, Nelson SF, Nievergelt CM, Nikolovq I, Nimgaonkar V, Nolen WA, Nöthen MM, Nwulia EA, Nyholt DR, O'Donovan MC, O'Dushlaine C, Oades RD, Olincy A, Olsen L, Ophoff RA, Osby U, Óskarsson H, Owen MJ, Palotie A, Pato MT, Pato CN, Penninx BP, Pergadia ML, Petursson H, Pickard BS, Pimm J, Piven J, Porgeirsson P, Posthuma D, Potash JB, Propping J, Puri V, Quested D, Quinn EM, Rasmussen HB, Raychaudhuri S, Rehnström K, Reif A, Rice J, Rossin L, Rothenberger A, Rouleau G, Ruderfer D, Rujescu D, Sanders AR, Schalling M, Schatzberg AF, Schftner WA, Schellenberg G, Schofield PR, Schork NJ, Schumacher J, Schwarz MM, Scolnick E, Scott LJ, Shi J, Shillling PD, Shyn SI, Sigurdsson E, Silverman JM, Sklar P, Slager SL, Smalley SL, Smit JH, Smith EN, Sonuga-Barke E, St Clair D, State M, Stefansson K, Stefansson H, Steffans M, Steinberg S, Steinhausen HC, Strauss J, Strohmaier J, Stroup TS, Sutcliffe J, Szatmari P, Szelinger S, Thirumalai S, Thompson RC, Tozzi F, Treutlein J, Uhr M, van den Oord EJ, Van Grootheest G, Vieland V, Vincent JB, Visscher PM, Watson SJ, Weissman MM, Werge T, Wienker TF, Willemsen G, Williamson R, Witt SH, Wray NR, Wright A, Xu W, Young AH, Zammit S, Zandi PP, Zhang P, Zitman FG, Zöllner S, Craddock N, Kendler K. (2013). Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet *381*, 1371-1379.

Davydov, E., Goode DL, Sirota M, Cooper GM, Sidow A, Batzoglou S. (2010). Identifying a high fraction of the human genome to be under selective constraint using GERP++. PLoS Comput Biol *6*, e1001025.

Demontis, D., Walters, Raymond K., Martin, Joanna, Mattheisen, Manuel, Als, Thomas Damm, Agerbo, Esben, Baldursson, Gísli, Belliveau, Rich, Bybjerg-Grauholm, Jonas, Bækvad-Hansen, Marie, Cerrato, Felecia, Chambert, Kimberly, Churchhouse, Claire, Dumont, Ashley, Eriksson, Nicholas, Gandal, Michael, Goldstein, Jacqueline, Grasby, Katrina L., Grove, Jakob, Gudmundsson, Olafur O., Hansen, Christine S., Hauberg, Mads Engel, Hollegaard, Mads V., Howrigan, Daniel P., Huang, Hailiang, Maller, Julian, Martin, Alicia R., Martin, Nicholas G., Moran, Jennifer, Pallesen, Jonatan, Palmer, Duncan S., Bøcker Pedersen, Carsten, Giørtz Pedersen, Marianne, Poterba, Timothy, Buchhave

Poulsen, Jesper, Ripke, Stephan, Robinson, Elise B., Satterstrom, F. Kyle, Stefansson, Hreinn, Stevens, Christine, Turley, Patrick, Walters, G. Bragi, Won, Hyejung, Wright, Margaret J., Andreassen, Ole A., Asherson, Philip, Burton, Christie, Boomsma, Bru, Dalsgaard, Soren, Franke, Barbara, Gelernter, Joel, Geschwind, Daniel, Hakonarson, Hakon, Haavik, Jan, Kranzler, Henry, Kuntsi, Jonna, Langley, Kate, Lesch, Klaus-Peter, Middeldorp, Christel, Reif, Andreas, Rohde, Luis Augusto, Roussos, Panos, Schacha, Russell, Sklar, Pamela, Sonuga-Barke, Edmund, Sullivan, Patrick F., Thapar, Anita, Tung, Joyce, Waldman, Irwin, Medland, Sarah E., Stefansson, Kari, Nordentoft, Merete, Hougaard, David M., Werge, Thomas, Mors, Ole, Bo Mortensen, Preben, Daly, Mark J., Faraone, Stephen V., Børglum, Anders D. and Neale, Benjamin M. 2018. Discovery of the first genome-wide significant risk loci for attention-deficit/hyperactivity disorder. Nature Genetics (2018). Discovery of the first genome-wide significant risk loci for attention-deficit/hyperactivity disorder. Nat Genet *In Press*.

Duncan, L., Yilmaz Z, Gaspar H, Walters R, Goldstein J, Anttila V, Bulik-Sullivan B, Ripke S; Eating Disorders Working Group of the Psychiatric Genomics Consortium, Thornton L, Hinney A, Daly M, Sullivan PF, Zeggini E, Breen G, Bulik CM. (2017). Significant Locus and Metabolic Genetic Correlations Revealed in Genome-Wide Association Study of Anorexia Nervosa. Am J Psychiatry *174*.

Duncan, L.E., Ratanatharathorn, A., Aiello, A.E., Almli, L.M., Amstadter, A.B., Ashley-Koch, A.E., Baker, D.G., Beckham, J.C., Bierut, L.J., Bisson, J.*, et al.* (2018). Largest GWAS of PTSD (N=20 070) yields genetic overlap with schizophrenia and sex differences in heritability. Mol Psychiatry *23*, 666-673.

Elia, J., Gai X, Xie HM, Perin JC, Geiger E, Glessner JT, D'arcy M, deBerardinis R, Frackelton E, Kim C, Lantieri F, Muganga BM, Wang L, Takeda T, Rappaport EF, Grant SF, Berrettini W, Devoto M, Shaikh TH, Hakonarson H, White PS. (2010). Rare structural variants found in attention-deficit hyperactivity disorder are preferentially associated with neurodevelopmental genes. Mol Psychiatry *15*, 637-646.

Gorsuch, R. (1988). Exploratory Factor Analysis. In Handbook of Multivariate Experimental Psychology Perspectives on Individual Differences, J.R. Nesselroade, Cattell R.B. , ed. (Boston, MA: Springer), pp. 231-258.

Goyette, P., Boucher, G., Mallon, D., Ellinghaus, E., Jostins, L., Huang, H., Ripke, S., Gusareva, E.S., Annese, V., Hauser, S.L.*, et al.* (2015). High-density mapping of the MHC identifies a shared role for HLA-DRB1*01:03 in inflammatory bowel diseases and heterozygous advantage in ulcerative colitis. Nat Genet *47*, 172-179.

Grantyn, R., Grantyn AA (1973). Postsynaptic responses of hippocampal neurons to mesencephalic stimulation: depolarizing potentials and discharge patterns. Brain Res *53*, 55-69.

Grotzinger, A.D., Rhemtulla, M., de Vlaming, R., Ritchie, S. J., Mallard, T. T., Hill, W. D., ..., Nivard, M. G., & Tucker-Drob, E. M. (2018). Genomic SEM Provides Insights into the Multivariate Genetic Architecture of Complex Traits. bioRxiv.

Grove, J., Ripke S, Als TD, Mattheisen M, Walters R, et al. (2017). Common risk variants identified in autism spectrum disorder. biorxiv.

Hamada N, I.H., Iwamoto I, Morishita R, Tabata H, Nagata K (2015). Role of the cytoplasmic isoform of RBFOX1/A2BP1 in establishing the architecture of the developing cerebral cortex. Mol Autism *6*.

Hamada N, I.H., Nishijo T, et al. (2016). Essential role of the nuclear isoform of RBFOX1, a candidate gene for autism spectrum disorders, in the brain development. Scientific reports.

Han, B., and Eskin, E. (2012). Interpreting meta-analyses of genome-wide association studies. PLoS genetics *8*, e1002555.

Hill, W., Zhang XS (2012). Assessing pleiotropy and its evolutionary consequences: pleiotropy is not necessarily limited, nor need it hinder the evolution of complexity. Nat Rev Genet *13*, 296.

Horton, J.R., Upadhyay A.K., Qi H.H., Zhang X., Shi Y., Cheng X. (2010). Enzymatic and structural insights for substrate specificity of a family of jumonji histone lysine demethylases.". Nat Struct Mol Biol *17*, 38-43.

Huang, H., Fang, M., Jostins, L., Umicevic Mirkov, M., Boucher, G., Anderson, C.A., Andersen, V., Cleynen, I., Cortes, A., Crins, F.*, et al.* (2017). Fine-mapping inflammatory bowel disease loci to single-variant resolution. Nature *547*, 173-178.

International League Against Epilepsy Consortium on Complex Epilepsies. Electronic address, e.-a.u.e.a. (2014). Genetic determinants of common epilepsies: a meta-analysis of genome-wide association studies. Lancet Neurol *13*, 893-903.

International Obsessive Compulsive Disorder Foundation Genetics Collaborative (IOCDF-GC) and OCD Collaborative Genetics Association Studies (OCGAS) (2017). Revealing the complex genetic architecture of obsessive compulsive disorder using meta-analysis. Mol Psychiatry *23*, 1181-1188.

Jamuar, S., Schmitz-Abe K, D'Gama AM, Drottar M, Chan WM, Peeva M, Servattalab S, Lam AN, Delgado MR, Clegg NJ, Zayed ZA, Dogar MA, Alorainy IA, Jamea AA, Abu-Amero K, Griebel M, Ward W, Lein ES, Markianos K, Barkovich AJ, Robson CD, Grant PE, Bosley TM, Engle EC, Walsh CA, Yu TW (2017). Biallelic mutations in human DCC cause developmental split-brain syndrome. Nat Genet *49*, 606-612.

Jones, S.E., Tyrrell, J., Wood, A.R., Beaumont, R.N., Ruth, K.S., Tuke, M.A., Yaghootkar, H., Hu, Y., Teder-Laving, M., Hayward, C.*, et al.* (2016). Genome-Wide Association Analyses in 128,266 Individuals Identifies New Morningness and Sleep Duration Loci. PLoS Genet *12*, e1006125.

Kiezun, A., Pulit SL, Francioli LC, van Dijk F, Swertz M, Boomsma DI, van Duijn CM, Slagboom PE, van Ommen GJ, Wijmenga C; Genome of the Netherlands Consortium, de Bakker PI, Sunyaev SR. (2013). Deleterious alleles in the human genome are on average younger than neutral alleles of the same frequency. PLoS Genet *9*, e1003301.

Lambert, J.C., Ibrahim-Verbaas, C.A., Harold, D., Naj, A.C., Sims, R., Bellenguez, C., DeStafano, A.L., Bis, J.C., Beecham, G.W., Grenier-Boley, B.*, et al.* (2013). Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet *45*, 1452-1458.

Liu, J.Z., van Sommeren, S., Huang, H., Ng, S.C., Alberts, R., Takahashi, A., Ripke, S., Lee, J.C., Jostins, L., Shah, T.*, et al.* (2015). Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. Nat Genet *47*, 979-986.

Malik, R., Traylor, M., Pulit, S.L., Bevan, S., Hopewell, J.C., Holliday, E.G., Zhao, W., Abrantes, P., Amouyel, P., Attia, J.R.*, et al.* (2016). Low-frequency and common genetic variation in ischemic stroke: The METASTROKE collaboration. Neurology *86*, 1217-1226.

Manitt C, E.C., Pokinko M, et al. (2013). Dcc orchestrates the development of the prefrontal cortex during adolescence and is altered in psychiatric patients. Transl Psychiatry.

Marsh, A., Heron D, Edwards TJ, Quartier A, Galea C, Nava C, Rastetter A, Moutard ML, Anderson V, Bitoun P, Bunt J, Faudet A, Garel C, Gillies G, Gobius I, Guegan J, Heide S, Keren B, Lesne F, Lukic V, Mandelstam SA, McGillivray G, McIlroy A, Méneret A, Mignot C, Morcom LR, Odent S, Paolino A, Pope K, Riant F, Robinson GA, Spencer-Smith M, Srour M, Stephenson SE, Tankard R, Trouillard O, Welniarz Q, Wood A, Brice A, Rouleau G, Attié-Bitach T, Delatycki MB, Mandel JL, Amor DJ, Roze E, Piton A, Bahlo M, Billette de Villemeur T, Sherr EH, Leventer RJ, Richards LJ, Lockhart PJ, Depienne C (2017). Mutations in DCC cause isolated agenesis of the corpus callosum with incomplete penetrance. Nat Genet *49*, 511-514.

Nikpay, M., Goel, A., Won, H.H., Hall, L.M., Willenborg, C., Kanoni, S., Saleheen, D., Kyriakou, T., Nelson, C.P., Hopewell, J.C.*, et al.* (2015). A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. Nat Genet *47*, 1121-1130.

Okbay, A., Baselmans, B.M., De Neve, J.E., Turley, P., Nivard, M.G., Fontana, M.A., Meddens, S.F., Linner, R.K., Rietveld, C.A., Derringer, J.*, et al.* (2016). Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. Nat Genet *48*, 624-633.

Otowa, T., Hek, K., Lee, M., Byrne, E.M., Mirza, S.S., Nivard, M.G., Bigdeli, T., Aggen, S.H., Adkins, D., Wolen, A.*, et al.* (2016). Meta-analysis of genome-wide association studies of anxiety disorders. Mol Psychiatry *21*, 1485.

Pollard, K., Hubisz MJ, Rosenbloom KR, Siepel A (2010). Detection of nonneutral substitution rates on mammalian phylogenies. Genome Res *20*, 110-121.

Qi, H.H., Sarkissian M., Hu G.Q., Wang Z., Bhattacharjee A., Gordon D.B., Gonzales M., Lan F., Ongusaha P.P., Huarte M., Yaghi N.K., Lim H., Garcia B.A., Brizuela L., Zhao K., Roberts T.M., Shi Y (2010). Histone H4K20/H3K9 demethylase PHF8 regulates zebrafish brain and craniofacial development. Nature *466*, 503-507.

Schizophrenia Working Group of the Psychiatric Genomics Consortium, Ripke S, Neale BM, Corvin A, Walters JT, Farh KH, Holmans PA, Lee PH, Bulik-Sullivan B, Collier DA, Huang H, Pers TH, Agartz I, Agerbo E, Albus M, Alexander M, Amin F, Bacanu SA, Begemann M, Belliveau RA Jr, Bene J, Bergen SE, Bevilacqua E, Bigdeli TB, Black DW, Bruggeman R, Buccola NG, Buckner RL, Byerley W, Cahn W, Cai G, Campion D, Cantor RM, Carr VJ, Carrera N, Catts SV, Chambert KD, Chan RC, Chen RY, Chen EY, Cheng W, Cheung EF, Chong SA, Cloninger CR, Cohen D, Cohen N, Cormican P, Craddock N, Crowley JJ, Curtis D, Davidson M, Davis KL, Degenhardt F, Del Favero J, Demontis D, Dikeos D, Dinan T, Djurovic S, Donohoe G, Drapeau E, Duan J, Dudbridge F, Durmishi N, Eichhammer P, Eriksson J, Escott-Price V, Essioux L, Fanous AH, Farrell MS, Frank J, Franke L, Freedman R, Freimer NB, Friedl M, Friedman JI, Fromer M, Genovese G, Georgieva L, Giegling I, Giusti-Rodríguez P, Godard S, Goldstein JI, Golimbet V, Gopal S, Gratten J, de Haan L, Hammer C, Hamshere ML, Hansen M, Hansen T, Haroutunian V, Hartmann AM, Henskens FA, Herms S, Hirschhorn JN, Hoffmann P, Hofman A, Hollegaard MV, Hougaard DM, Ikeda M, Joa I, Julià A, Kahn RS, Kalaydjieva L, Karachanak-Yankova S, Karjalainen J, Kavanagh D, Keller MC, Kennedy JL, Khrunin A, Kim Y, Klovins J, Knowles JA, Konte B, Kucinskas V, Ausrele Kucinskiene Z, Kuzelova-Ptackova H, Kähler AK, Laurent C, Keong JL, Lee SH, Legge SE, Lerer B, Li M, Li T, Liang KY, Lieberman J, Limborska S, Loughland CM, Lubinski J, Lönnqvist J, Macek M Jr, Magnusson PK, Maher BS, Maier W, Mallet J, Marsal S, Mattheisen M, Mattingsdal M, McCarley RW, McDonald C, McIntosh AM, Meier S, Meijer CJ, Melegh B, Melle I, Mesholam-Gately RI, Metspalu A, Michie PT, Milani L, Milanova V, Mokrab Y, Morris DW, Mors O, Murphy KC, Murray RM, Myin-Germeys I, Müller-Myhsok B, Nelis M, Nenadic I, Nertney DA, Nestadt G, Nicodemus KK, Nikitina-Zake L, Nisenbaum L, Nordin A, O'Callaghan E, O'Dushlaine C, O'Neill FA, Oh SY, Olincy A, Olsen L, Van Os J, Pantelis C, Papadimitriou GN, Papiol S, Parkhomenko E, Pato MT, Paunio T, Pejovic-Milovancevic M, Perkins DO, Pietiläinen O, Pimm J, Pocklington AJ, Powell J, Price A, Pulver AE, Purcell SM, Quested D, Rasmussen HB, Reichenberg A, Reimers MA, Richards AL, Roffman JL, Roussos P, Ruderfer DM, Salomaa V, Sanders AR, Schall U, Schubert CR, Schulze TG, Schwab SG, Scolnick EM, Scott RJ, Seidman LJ, Shi J, Sigurdsson E, Silagadze T, Silverman JM, Sim K, Slominsky P, Smoller JW, So HC, Spencer CA, Stahl EA, Stefansson H, Steinberg S, Stogmann E, Straub RE, Strengman E, Strohmaier J, Stroup TS, Subramaniam M, Suvisaari J, Svrakic DM, Szatkiewicz JP, Söderman E, Thirumalai S, Toncheva D, Tosato S, Veijola J, Waddington J, Walsh D, Wang D, Wang Q, Webb BT, Weiser M, Wildenauer DB, Williams NM, Williams S, Witt SH, Wolen AR, Wong EH, Wormley BK, Xi HS, Zai CC, Zheng X, Zimprich F, Wray NR, Stefansson K, Visscher PM, Adolfsson R, Andreassen OA, Blackwood DH, Bramon E, Buxbaum JD, Børglum AD, Cichon S, Darvasi A, Domenici E, Ehrenreich H, Esko T, Gejman PV, Gill M, Gurling H, Hultman CM, Iwata N, Jablensky AV, Jönsson EG, Kendler KS, Kirov G, Knight J, Lencz T, Levinson DF, Li QS, Liu J, Malhotra AK, McCarroll SA, McQuillin A, Moran JL, Mortensen PB, Mowry BJ, Nöthen MM, Ophoff RA, Owen MJ, Palotie A, Pato CN, Petryshen TL, Posthuma D, Rietschel M, Riley BP, Rujescu D, Sham PC, Sklar P, St Clair D, Weinberger DR, Wendland JR, Werge T, Daly MJ, Sullivan PF, O'Donovan MC. (2014). Biological insights from 108 schizophrenia-associated genetic loci. Nature *511*, 421-427.

Sebat, J., Lakshmi B, Malhotra D, Troge J, Lese-Martin C, Walsh T, Yamrom B, Yoon S, Krasnitz A, Kendall J, Leotta A, Pai D, Zhang R, Lee YH, Hicks J, Spence SJ, Lee AT, Puura K, Lehtimäki T, Ledbetter D, Gregersen PK, Bregman J, Sutcliffe JS, Jobanputra V, Chung W, Warburton D, King MC, Skuse D, Geschwind DH, Gilliam TC, Ye K, Wigler M. (2007). Strong association of de novo copy number mutations with autism. Science *316*, 445-449.

Siepel, A., Bejerano G, Pedersen JS, Hinrichs AS, Hou M, Rosenbloom K, Clawson H, Spieth J, Hillier LW, Richards S, Weinstock GM, Wilson RK, Gibbs RA, Kent WJ, Miller W, Haussler D (2005).

Evolutionarily conserved elements in vertebrate, insect, worm, and yeast genomes. Genome Res *15*, 1034-1050.

Smoller, J., Andreassen OA, Edenberg HJ, Faraone SV, Glatt SJ, Kendler KS. (2018). Psychiatric genetics and the structure of psychopathology. Mol Psychiatry.

Stahl, E., Breen G, Forstner, A, McQuilin, A, Ripke S, Bipolar Disorder Working Group of the Psychiatric Genomics Consortium, Cichon S, Scott L, Ophoff R, Andreassen OA, Kelsoe J, Sklar P (2018). Genomewide association study identifies 30 loci associated with bipolar disorder. bioRxiv.

Topchiy, E., Panzhinskiy E, Griffin WS, Barger SW, Das M, Zawada WM. (2013). Nox4-generated superoxide drives angiotensin II-induced neural stem cell proliferation. . Dev Neurosci *35*, 293-305.

Tsukada, Y., Ishitani T., Nakayama K.I. (2010). KDM7 is a dual demethylase for histone H3 Lys 9 and Lys 27 and functions in brain development. Genes Dev *24*, 432-437.

Won, H., de la Torre-Ubieta L, Stein JL, Parikshak NN, Huang J, Opland CK, Gandal MJ, Sutton GJ, Hormozdiari F, Lu D, Lee C, Eskin E, Voineagu I, Ernst J, Geschwind DH. (2016). Chromosome conformation elucidates regulatory relationships in developing human brain. Nature *538*, 523-527.

Woo, D., Falcone, G.J., Devan, W.J., Brown, W.M., Biffi, A., Howard, T.D., Anderson, C.D., Brouwers, H.B., Valant, V., Battey, T.W.*, et al.* (2014). Meta-analysis of genome-wide association studies identifies 1q22 as a susceptibility locus for intracerebral hemorrhage. Am J Hum Genet *94*, 511-521.

Wood, A.R., Esko, T., Yang, J., Vedantam, S., Pers, T.H., Gustafsson, S., Chu, A.Y., Estrada, K., Luan, J., Kutalik, Z.*, et al.* (2014). Defining the role of common variation in the genomic and biological architecture of adult human height. Nat Genet *46*, 1173-1186.

Wray, N., Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, Adams MJ, Agerbo E, Air TM, Andlauer TMF, Bacanu SA, Bækvad-Hansen M, Beekman AFT, Bigdeli TB, Binder EB, Blackwood DRH, Bryois J, Buttenschøn HN, Bybjerg-Grauholm J, Cai N, Castelao E, Christensen JH, Clarke TK, Coleman JIR, Colodro-Conde L, Couvy-Duchesne B, Craddock N, Crawford GE, Crowley CA, Dashti HS, Davies G, Deary IJ, Degenhardt F, Derks EM, Direk N, Dolan CV, Dunn EC, Eley TC, Eriksson N, Escott-Price V, Kiadeh FHF, Finucane HK, Forstner AJ, Frank J, Gaspar HA, Gill M, Giusti-Rodríguez P, Goes FS, Gordon SD, Grove J, Hall LS, Hannon E, Hansen CS, Hansen TF, Herms S, Hickie IB, Hoffmann P, Homuth G, Horn C, Hottenga JJ, Hougaard DM, Hu M, Hyde CL, Ising M, Jansen R, Jin F, Jorgenson E, Knowles JA, Kohane IS, Kraft J, Kretzschmar WW, Krogh J, Kutalik Z, Lane JM, Li Y, Li Y, Lind PA, Liu X, Lu L, MacIntyre DJ, MacKinnon DF, Maier RM, Maier W, Marchini J, Mbarek H, McGrath P, McGuffin P, Medland SE, Mehta D, Middeldorp CM, Mihailov E, Milaneschi Y, Milani L, Mill J, Mondimore FM, Montgomery GW, Mostafavi S, Mullins N, Nauck M, Ng B, Nivard MG, Nyholt DR, O'Reilly PF, Oskarsson H, Owen MJ, Painter JN, Pedersen CB, Pedersen MG, Peterson RE, Pettersson E, Peyrot WJ, Pistis G, Posthuma D, Purcell SM, Quiroz JA, Qvist P, Rice JP, Riley BP, Rivera M, Saeed Mirza S, Saxena R, Schoevers R, Schulte EC, Shen L, Shi J, Shyn SI, Sigurdsson E, Sinnamon GBC, Smit JH, Smith DJ, Stefansson H, Steinberg S, Stockmeier CA, Streit F, Strohmaier J, Tansey KE, Teismann H, Teumer A, Thompson W, Thomson PA, Thorgeirsson TE, Tian C, Traylor M, Treutlein J, Trubetskoy V, Uitterlinden AG, Umbricht D, Van der Auwera S, van Hemert AM, Viktorin A, Visscher PM, Wang Y, Webb BT, Weinsheimer SM, Wellmann J, Willemsen G, Witt SH, Wu Y, Xi HS, Yang J, Zhang F; eQTLGen; 23andMe, Arolt V, Baune BT, Berger K, Boomsma DI, Cichon S, Dannlowski U, de Geus ECJ, DePaulo JR, Domenici E, Domschke K, Esko T, Grabe HJ, Hamilton SP, Hayward C, Heath AC, Hinds DA, Kendler KS, Kloiber S, Lewis G, Li QS, Lucae S, Madden PFA, Magnusson PK, Martin NG, McIntosh AM, Metspalu A, Mors O, Mortensen PB, Müller-Myhsok B, Nordentoft M, Nöthen MM, O'Donovan MC, Paciga SA, Pedersen NL, Penninx BWJH, Perlis RH, Porteous DJ, Potash JB, Preisig M, Rietschel M, Schaefer C, Schulze TG, Smoller JW, Stefansson K, Tiemeier H, Uher R, Völzke H, Weissman MM, Werge T, Winslow AR, Lewis CM, Levinson DF, Breen G, Børglum AD, Sullivan PF; Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. (2018). Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nature Genetics *50*, 668-681.

Xu, B., Roos JL, Levy S, Van Rensburg EJ, Gogos JA, Karayiorgou M (2008). Strong association of de novo copy number mutations with sporadic schizophrenia. Nat Genet *40*, 880-885.

Yang, J., Ferreira, T., Morris, A.P., Medland, S.E., Genetic Investigation of, A.T.C., Replication, D.I.G., Meta-analysis, C., Madden, P.A., Heath, A.C., Martin, N.G., *et al.* (2012). Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. Nat Genet *44*, 369-375, S361-363.

Yang, J., Ferreira T, Morris AP, Medland SE; Genetic Investigation of ANthropometric Traits (GIANT) Consortium; DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium, Madden PA, Heath AC, Martin NG, Montgomery GW, Weedon MN, Loos RJ, Frayling TM, McCarthy MI, Hirschhorn JN, Goddard ME, Visscher PM. (2012). Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. Nat Genet *44*, 369-375.

Zheng, J., Erzurumluoglu, A.M., Elsworth, B.L., Kemp, J.P., Howe, L., Haycock, P.C., Hemani, G., Tansey, K., Laurin, C., Early, G.*, et al.* (2017). LD Hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. Bioinformatics *33*, 272-279.

OBJ

OBJ

Figure Legends

Figure 1. Genetic relationship between eight neuropsychiatric disorders. (A) SNP-based genetic correlations (r_g) were estimated between eight neuropsychiatric disorders using LDSC. The size of the circles scales with the significance of the p-values. The darker the color, the larger the magnitude of r_g. Star sign (*) indicates statistical significance after Bonferroni correction. ADHD: attention-deficit/hyperactivity disorder; AN: anorexia nervosa; ASD: autism spectrum disorder; BIP: bipolar disorder; OCD: obsessive compulsive disorder; SCZ: schizophrenia. (B) SNP-based genetic correlations between eight disorders were depicted using an undirected graph to reveal complex genetic relationships than pairwise. Only significant genetic correlations in (A) were displayed. Each node represents a particular disorder, with edges indicating the strength of the pairwise correlations. The width of the edges increases, while the length decreases, with the absolute values of r_g. (C) Based on results of an exploratory factor analysis of the genetic correlation matrix, a confirmatory factor model with three correlated genetic factors was specified using Genomic SEM and estimated with the weighted least squares algorithm. Two-headed arrows connecting the three factors to one another represent their correlations. Two-headed arrows connecting the genetic components of the individual psychiatric disorders to themselves represent residual genetic variances, and correspond to the proportion of heritable variation in liability to each individual psychiatric disorder that is unexplained by the three factors. Standardized parameters are depicted with their standard errors in parentheses. Paths labeled 1 with no standard errors reported are fixed parameters, which are used for scaling.

Figure 2. Results of cross-disorder meta-analysis and candidate gene mapping. (A) Quantile-quantile (QQ) plot displaying the observed meta-analysis statistics vs. the expected ones under the null model of no associations in the $-\log_{10}$(p-value) scale. Although a marked departure is notable between the two statistics, the estimated lambda_{1000} and the estimated LD Score regression intercept indicate that the observed inflation is mainly due to polygenic signals rather than major confounding factors including population stratification. (B) Gene prioritization strategies for associated locus. Candidate genes were mapped on each locus if index SNP and credible SNPs reside within a protein-coding gene, are eQTL markers of the gene in the brain tissue, or interact with promoter regions of the gene based on brain Hi-C data. (C) Manhattan plot displaying the cross-disorder meta-analysis results highlighted with candidate genes mapped to top pleiotropic regions.

Figure 3. Prediction of disorder-specific associations for illustrative pleiotropic loci: (A) rs8084351 on 18q21.2; (B) rs7193263 on 16p13.3; (C) rs117956829 on 11q14.3; and (D) rs10265001 on 7q34. Results are presented for the two most pleiotropic loci (**A, B**) and two highly pleiotropic novel loci (**C,D**) For each locus, disorder-specific effects of the index SNP were presented using ForestPMPlot. The first panel is the forest plot, displaying disorder-specific association p-value, log odds ratio (OR), and standard errors of the SNP. The meta-analysis p-value and the corresponding summary statistic are displayed on the top and the bottom of the forest plot, respectively. The second panel is the PM-plot, in which the X-axis represents the m-value, the posterior probability that the effect exists in each disorder, and the Y-axis represents the disorder-specific association p-value as $-\log_{10}$(p-value). Disorders are depicted as a dot, of which the size represents the sample size of an individual GWAS. Disorders with an estimated m-value $\geq$ 0.9 are colored in red, while those with an m-value < 0.9 are marked in green.

Figure 4. Eleven loci with opposite directional effects. The radius of each wedge corresponds to the absolute values of the Z-scores (log(Odds ratio)/S.E) obtained from association tests of the SNP for eight disorders. The color indicates whether the examined SNP carries risk (red) or protective effects (green) for each disorder.

Figure 5. Results of functional genomics data analysis for pleiotropic vs. disorder-specific loci. (A) GTEX tissue-specific enrichment results for 109 pleiotropic risk loci. (B) Average gene-expression in brain cortical regions is depicted based on the pleiotropy level of the associated genes. The 147 genome-wide significant loci from the cross-disorder meta analysis were clustered into three groups based on predicted disorder-specific associations: (1) no-pleiotropy, (2) pleiotropy=2, and (3) pleiotropy>2. The “no-pleiotropy” group included 37 loci that showed a single-disorder-specific

association, while the “pleiotropy=2” and “pleiotropy>2” groups included 60 and 49 loci that are associated with two and more than two disorders, respectively. (C) Brain developmental expression trajectory displayed for the three groups of genes based on the BrainSpan data. (D) Cortical regional enrichments calculated for the three gene groups. (E) Cell-type specific enrichment analysis results.

Baurecht, H., Hotze, M., Brand, S., Buning, C., Cormican, P., Corvin, A., Ellinghaus, D., Ellinghaus, E., Esparza-Gordillo, J., Folster-Holst, R*., et al.* (2015). Genome-wide comparative analysis of atopic dermatitis and psoriasis gives insight into opposing genetic mechanisms. Am J Hum Genet *96*, 104-120.

Bendriem, R.M., and Ross, M.E. (2017). Wiring the Human Brain: A User's Handbook. Neuron *95*, 482-485.

Bhattacharjee, S., Rajaraman, P., Jacobs, K.B., Wheeler, W.A., Melin, B.S., Hartge, P., GliomaScan, C., Yeager, M., Chung, C.C., Chanock, S.J*., et al.* (2012). A subset-based approach improves power and interpretation for the combined analysis of genetic association studies of heterogeneous traits. Am J Hum Genet *90*, 821-835.

Bipolar, D., Schizophrenia Working Group of the Psychiatric Genomics Consortium. Electronic address, d.r.v.e., Bipolar, D., and Schizophrenia Working Group of the Psychiatric Genomics, C. (2018). Genomic Dissection of Bipolar Disorder and Schizophrenia, Including 28 Subphenotypes. Cell *173*, 1705-1715 e1716.

Brainstorm, C., Anttila, V., Bulik-Sullivan, B., Finucane, H.K., Walters, R.K., Bras, J., Duncan, L., Escott-Price, V., Falcone, G.J., Gormley, P*., et al.* (2018). Analysis of shared heritability in common disorders of the brain. Science *360*.

Caspi, A., Houts, R.M., Belsky, D.W., Goldman-Mellor, S.J., Harrington, H., Israel, S., Meier, M.H., Ramrakha, S., Shalev, I., Poulton, R*., et al.* (2014). The p Factor: One General Psychopathology Factor in the Structure of Psychiatric Disorders? Clin Psychol Sci *2*, 119-137.

Cross-Disorder Group of the Psychiatric Genomics, C., Lee, S.H., Ripke, S., Neale, B.M., Faraone, S.V., Purcell, S.M., Perlis, R.H., Mowry, B.J., Thapar, A., Goddard, M.E*., et al.* (2013). Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat Genet *45*, 984-994.

Demontis, D., Walters, R.K., Martin, J., Mattheisen, M., Als, T.D., Agerbo, E., Baldursson, G., Belliveau, R., Bybjerg-Grauholm, J., Baekvad-Hansen, M*., et al.* (2018). Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat Genet.

Disease, G.B.o., Injury, I., and Prevalence, C. (2017). Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet *390*, 1211-1259.

Gorsuch, R. (1988). Exploratory Factor Analysis. In Handbook of Multivariate Experimental Psychology Perspectives on Individual Differences, J.R. Nesselroade, and R.B. Cattell, eds. (Boston, MA: Springer), pp. 231-258.
Grotzinger, A., Rhemtulla, M., de Vlaming, R., Ritchie, S., Mallard, T., Hill, W., Ip HF, McIntosh, A., Deary, I.J., Koellinger, P.D.*, et al.* (2018). Genomic SEM provides insights into the multivariate genetic architecture of complex traits. BiorXiv *doi: https://doi.org/10.1101/305029*.
Grove, J., Ripke, S., Als, T.D., Mattheisen, M., Walters, R., Won, H., Pallesen, J., Agerbo, E., Andreassen, O.A., Anney, R.*, et al.* (2017). Common risk variants identified in autism spectrum disorder. bioRxiv.
Hoops, D., and Flores, C. (2017). Making Dopamine Connections in Adolescence. Trends Neurosci *40*, 709-719.
International Obsessive Compulsive Disorder Foundation Genetics, C., and Studies, O.C.D.C.G.A. (2018). Revealing the complex genetic architecture of obsessive-compulsive disorder using meta-analysis. Mol Psychiatry *23*, 1181-1188.
Jamuar, S.S., Schmitz-Abe, K., D'Gama, A.M., Drottar, M., Chan, W.M., Peeva, M., Servattalab, S., Lam, A.N., Delgado, M.R., Clegg, N.J.*, et al.* (2017). Biallelic mutations in human DCC cause developmental split-brain syndrome. Nat Genet *49*, 606-612.
Kessler, R.C., and Wang, P.S. (2008). The descriptive epidemiology of commonly occurring mental disorders in the United States. Annu Rev Public Health *29*, 115-129.
Lettre, G., and Rioux, J.D. (2008). Autoimmune diseases: insights from genome-wide association studies. Hum Mol Genet *17*, R116-121.
Liu, Y., Bhowmick, T., Liu, Y., Gao, X., Mertens, H.D.T., Svergun, D.I., Xiao, J., Zhang, Y., Wang, J.H., and Meijers, R. (2018). Structural Basis for Draxin-Modulated Axon Guidance and Fasciculation by Netrin-1 through DCC. Neuron *97*, 1261-1267 e1264.
Marsh, A.P., Heron, D., Edwards, T.J., Quartier, A., Galea, C., Nava, C., Rastetter, A., Moutard, M.L., Anderson, V., Bitoun, P.*, et al.* (2017). Mutations in DCC cause isolated agenesis of the corpus callosum with incomplete penetrance. Nat Genet *49*, 511-514.
Reynolds, L.M., Pokinko, M., Torres-Berrio, A., Cuesta, S., Lambert, L.C., Del Cid Pellitero, E., Wodzinski, M., Manitt, C., Krimpenfort, P., Kolb, B.*, et al.* (2018). DCC Receptors Drive Prefrontal Cortex Maturation by Determining Dopamine Axon Targeting in Adolescence. Biol Psychiatry *83*, 181-192.
Schizophrenia Working Group of the Psychiatric Genomics, C. (2014). Biological insights from 108 schizophrenia-associated genetic loci. Nature *511*, 421-427.
Schmitt, J., Schwarz, K., Baurecht, H., Hotze, M., Folster-Holst, R., Rodriguez, E., Lee, Y.A.E., Franke, A., Degenhardt, F., Lieb, W.*, et al.* (2016). Atopic dermatitis is associated with an increased risk for rheumatoid arthritis and inflammatory bowel disease, and a decreased risk for type 1 diabetes. J Allergy Clin Immunol *137*, 130-136.
Schork, A.J., Won, H., Appadurai, V., Nudel, R., Gandal, M., Delaneau, O., Hougaard, D., Baekved-Hansen, M., Bybjerg-Grauholm, J., Pedersen, M.G.*, et al.* (2017). A genome-wide association study for shared risk across major psychiatric disorders in a nation-wide birth cohort implicates fetal neurodevelopment as a key mediator. bioRxiv.
Smoller, J.W., Andreassen, O.A., Edenberg, H.J., Faraone, S.V., Glatt, S.J., and Kendler, K.S. (2018). Psychiatric genetics and the structure of psychopathology. Mol Psychiatry.
Solovieff, N., Cotsapas, C., Lee, P.H., Purcell, S.M., and Smoller, J.W. (2013). Pleiotropy in complex traits: challenges and strategies. Nat Rev Genet *14*, 483-495.
Stahl, E., Breen, G., Forstner, A., McQuillin, A., Ripke, S., Cichon, S., Scott, L., Ophoff, R., Andreassen, O.A., Kelsoe, J.*, et al.* (2018). Genomewide association study identifies 30 loci associated with bipolar disorder. bioRxiv, 173062.
Sullivan, P.F., Agrawal, A., Bulik, C.M., Andreassen, O.A., Borglum, A.D., Breen, G., Cichon, S., Edenberg, H.J., Faraone, S.V., Gelernter, J.*, et al.* (2018). Psychiatric Genomics: An Update and an Agenda. Am J Psychiatry *175*, 15-27.

Vosberg, D.E., Zhang, Y., Menegaux, A., Chalupa, A., Manitt, C., Zehntner, S., Eng, C., DeDuck, K., Allard, D., Durand, F.*, et al.* (2018). Mesocorticolimbic Connectivity and Volumetric Alterations in DCC Mutation Carriers. J Neurosci *38*, 4655-4665.
Wray, N.R., Ripke, S., Mattheisen, M., Trzaskowski, M., Byrne, E.M., Abdellaoui, A., Adams, M.J., Agerbo, E., Air, T.M., Andlauer, T.M.F.*, et al.* (2018). Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet *50*, 668-681.
Yang, J., Ferreira, T., Morris, A.P., Medland, S.E., Madden, P.A., Heath, A.C., Martin, N.G., Montgomery, G.W., Weedon, M.N., Loos, R.J.*, et al.* (2012). Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. Nature genetics *44*, 369-375, S361-363.
Yu, D., Sul, J.H., Tsetsos, F., Nawaz, M.S., Huang, A.Y., Zelaya, I., Illmann, C., Osiecki, L., Darrow, S.M., Hirschtritt, M.E.*, et al.* (In press.). Interrogating the genetic determinants of Tourette syndrome and other tic disorders through genome-wide association studies. Am J Psychiatry.
Zhu, Z., Anttila, V., Smoller, J.W., and Lee, P.H. (2018). Statistical power and utility of meta-analysis methods for cross-phenotype genome-wide association studies. PLoS One *13*, e0193256.